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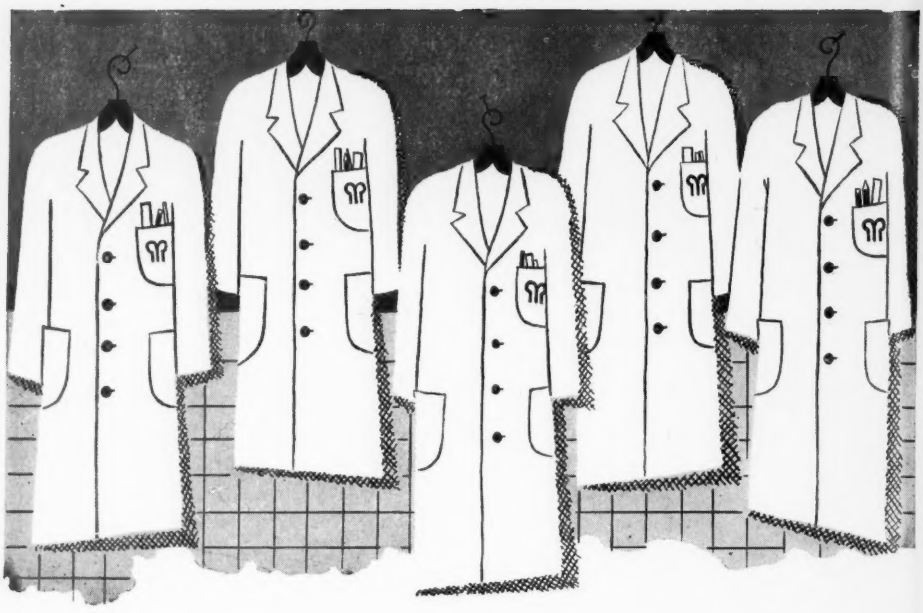

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FUNCTIONAL AND STRUCTURAL CHANGES CONSEQUENT TO HIGH DOSAGES OF RADIOACTIVE IODINE*†

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THERE is perhaps a natural feeling of urgency on the part of many laboratory and clinical workers which prompts the application of radioactive fission products to useful purposes. In adopting radioiodine as a tool for the selective and controlled destruction of cancerous or hyperactive thyroid tissue clinical medicine has far outstripped the laboratory experimentalists in the use of this powerful agent. The need for further information concerning the general and specific effects of highly radiant doses of radioactive iodine in the organism is apparent; the recognition of this need, if one may now judge from the published literature, has stimulated the institution of programs of study of radiation effects of radioiodine in many laboratories.

In this report it is our purpose to summarize the work of several years devoted to observation of sequelae in mice subsequent to administration

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Read at the Annual Meeting of the American Goiter Association, Houston, Texas, March 9, 1950.

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of high, "radiotoxic" dosages of the radioactive isotope, I^{131} (1,2, 3). Wherever feasible the relations of these results to the human organism will be indicated. It is hoped that some of the findings will give perspective and provide criteria against which the value of radioiodine in the therapy of clinical hyperthyroidism may be gauged. The advantages of radiant destruction of metastasized thyroidal carcinomas require no emphasis, because other methods have been found so ineffectual. On the other hand, in the treatment of hyperthyroidism for which a choice of several useful and successful alternatives is available, the use of radioiodine must now be submitted to careful evaluation (4).

Though they are obviously related, the phenomena observable subsequent to high dosage of I^{131} conveniently may be separated into two general groups: those located primarily in the thyroid or in its immediately contiguous structures, and those located in structures distant from the thyroid. Events in the thyroid area are virtually all consequences of the enormous β-radiation suicidally trapped by the thyroid in removing radioactive iodide from the blood for synthesis of thyroxine. Extrathyroidal happenings are of two kinds: those resulting from the relatively smaller quantities of radiation from I^{131} in the body fluids, and those which appear to grow out of the imbalances and endocrine and metabolic disturbances precipitated by radiation injuries. The last category of changes must also follow the direct radiation effects in time, and these alterations may be delayed by long intervals after the initial administration of radioiodine.

EFFECTS IN THE THYROID AND ADJACENT STRUCTURES

The thyroid-killing dose of I^{131}

The first actual demonstration of the thyroid-lethal properties of I^{131} appears in a review by J. G. Hamilton (1942 (5)). There is here illustrated, and briefly discussed, the thyroid of 1 of 2 dogs given 300 microcuries of I^{131} per kilo of body weight one hundred days before autopsy. The parathyroid remains, but the thyroid is replaced by a mass of fibers. The thyroidal radiation dose was estimated as 15,000–20,000 equivalent roentgens.

Aside from their intrinsic interest, determinations of actual thyroid-killing and thyroid-sparing dosages in experimental animals are data of primary need and significance to therapists employing I^{131}. Not only have these quantitative figures been lacking, but also important questions of a qualitative nature have yet to be answered. In a thyroid, partially destroyed by β-radiation to halt hyperthyroidism, will regeneration occur? If it does occur, what are the possibilities that it may be metaplastic or neoplastic?

Definite doses required to achieve certain degrees of thyroidal injury in experimental animals have begun to be recorded in the literature. Unfortu-

nately, many investigators, including the writer, merely supplied the doses given to the animal as a whole, in terms of millicuries or microcuries per kilogram body weight. This figure is meaningless, since the part of a dose that is actually taken up by the thyroid may vary from practically none to 80 or more per cent. The avidity of the thyroid for newly administered labelled iodine is profoundly affected by dietary iodine intake and the consequent plasma iodine level—facts which have been well established by animal and by clinical studies (6, 7).

We have tried to assay the thyroid-lethal dose in mice on three different dietary regimens (Table 1). In animals fed the commercial Rockland Chow

TABLE 1. THYROID-LETHAL CONCENTRATIONS OF I^{131} IN RELATION TO DIET

Diet	Thyroid-lethal dose, microcuries	Maximum thyroidal uptake, per cent	Average maximum I^{131} concentration, μc/mg.
Rockland Chow	—	1	—
Purina Chow	200	7.5	4.1
Modified Remington low-I diet	28	58	4.3

pellets, as much as 500 microcuries of I^{131} hardly affected the thyroid. Labelled iodine uptake on this diet is less than 1 per cent. The manufacturers of this food, for some reason, include KI as one ingredient. In animals fed Purina Chow, which contains moderate amounts of iodine, the thyroid-lethal dose is 200 microcuries; in animals fed a special low iodine diet it is 28 microcuries. When correction is made for the per cent uptake (6–7.5 per cent and 58 per cent, respectively) it is found that in each case the intrathyroidal lethal content of I^{131} is about 15 microcuries, or approximately 4 microcuries per milligram of thyroid tissue.

Examination of Figure 1 demonstrates that selection of the peak value of thyroidal I^{131} accumulation as a reference may give falsely high computations of the roentgen dosage. Especially with larger quantities of radioisotope, this peak is rapidly approached, and the retreat from it is almost as quick. The sharp break and reversal in I^{131} accumulation shown in these curves, would seem to indicate injury to some mechanism for iodine retention after certain concentrations of radioactivity have been attained. As might be expected, therefore, the break-point is reached more quickly, and the descent is sharper with the successively higher doses.

Some interesting facts regarding the time relations of thyroid injury by

I^{131} in mice have been obtained. The minimum thyroid-lethal dose (4 microcuries/milligram of thyroid = 4 millicuries/gram) requires between two and three weeks to kill all thyroid tissue. Larger doses kill more quickly. Doses of 20 microcuries per milligram of thyroid kill so quickly that within two days virtually all thyroid cells are necrotic.

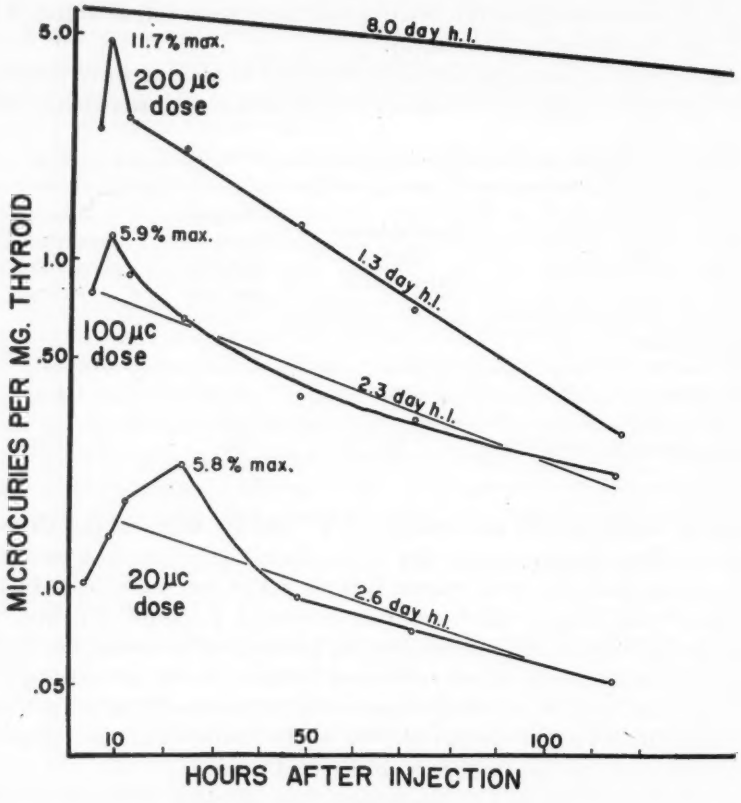

FIGURE 1

Some difficulty is encountered in calculating the equivalent roentgen dosage received by mouse thyroids killed by 4 microcuries/milligram thyroid concentrations of I^{131}. Marinelli, Quimby and Hine (8) have estimated that the maximum travel of β-particles of I^{131} in tissue is about 2 mm. The maximum thickness of the mouse thyroid is about 1.4 mm. and in most places, since the gland is rather leaf-shaped, it is less than 1 mm. thick. This means that a large fraction of the β-radiation trapped by the mouse

thyroid will dissipate its ionization in tissues outside the gland itself. By use of available formulae, designed for large human thyroids, it may be calculated that the r.e.p. (roentgen equivalent physical) delivered by the thyroid-lethal I^{131} dose is about 120,000. Actually, it must be somewhat less than this, since the calculations do not allow for extrathyroidal ionization. Feller *et al.* (9) have supplied a basis for computing the r.e.p. dose from trapped I^{131} in small (rat) thyroids. Even this scheme errs somewhat in assuming, for purposes of mathematical convenience, that the thyroid is spherical—a liberty that makes the morphologist wince. It would be much more accurate, no doubt, to assume a disc shape, or at least a series of smaller spheres.

The facts implied in the short tissue-range of β-particles of I^{131} serve to account for the geometric pattern of death of follicles in irradiated thyroids in mice. The first follicles to die are those in the thickest masses of glandular tissue. The last to die are those at the apices of the gland, and in the thin isthmus. At these positions the r.e.p. received by individual cells must be far less than in thick places since a very large proportion of β-particle ionization occurs in surrounding nonthyroidal tissues (9). This explains why it is that in mice, even doses of I^{131} much less than thyroid-lethal, usually destroy some deeply placed follicles, and why the remnants which survive sublethal doses are always from the cranial apex and isthmus of the gland.

There is, thus, a wide range of thyroid-killing doses of radioiodine, which destroy progressively larger fractions of the gland. We have reserved the term "thyroid-lethal dose" to characterize the minimum quantity which causes complete thyroidal destruction. The same phenomena must be considered to apply even if in altered scale, to human thyroid at edges, in small lobules and tags (as along the thyroglossal tract) and in small metastases of thyroid tumor.

Thyroidal histopathology of radiation from I^{131}

The largest doses of I^{131} produce the simplest histopathologic picture, a uniform destruction of follicles throughout the thyroid. Radiation death is so rapid that, although after forty-eight to seventy-two hours cells are amorphous in structure, densely eosinophilic in staining affinity and have lost stainability in their nuclei, they are still arranged as "ghost" follicles (Fig. 5). Shortly after irradiation no leucocytes or macrophages can be found within this mass of dead tissue, although they, as well as mast cells, are numerous at its edge. It is certainly possible that many such migratory cells have entered the still strongly radioactive mass and have lost their lives at the call of duty. The walls of larger intrathyroidal blood vessels are completely hyalinized, but even in this lifeless condition they appear to

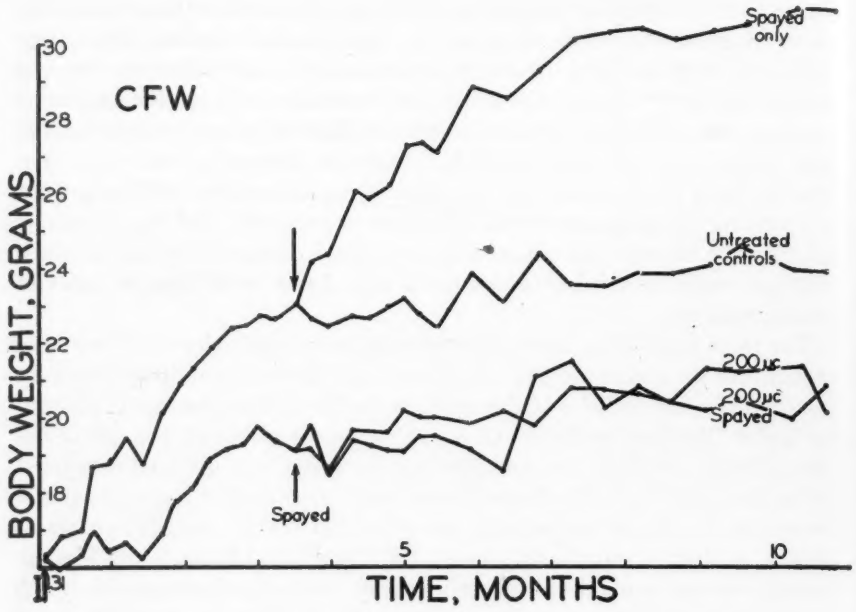

FIGURE 2

function successfully as conduits for blood for several days. After one week, rapid macrophagic activity and fibrosis quickly replace the thyroid tissue with edematous connective tissue. This then shrinks, within the second

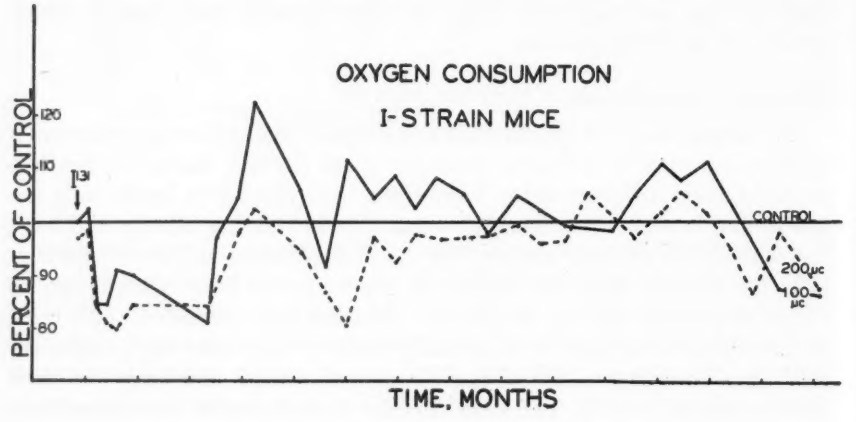

FIGURE 3

week, to leave a rather dense fibrous scar on the trachea in the place of the lost thyroid gland (Fig. 6).

Intrathyroidal doses of 4 to 8 microcuries of I^{131} per milligram of tissue ultimately kill all follicles also, but as implied previously, the pattern of destruction is more complex. The first visible microscopic changes, several days after treatment, are restricted zones of nuclear pyknosis deep in the thyroid, as well as a few intrafollicular hemorrhages. There is also a swelling of the endothelial cells of vascular channels. There follows a period, the

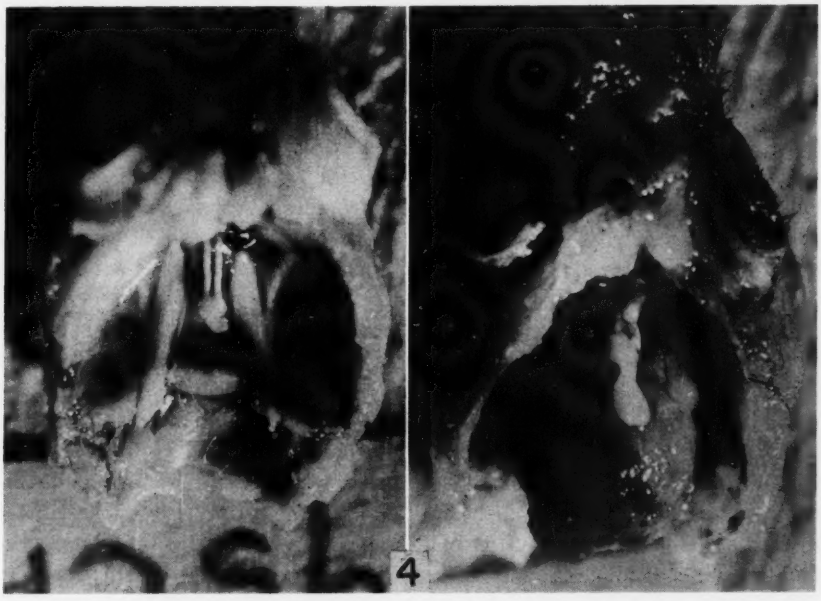

FIG. 4. Head of control mouse (left) and of I^{131}-injected mouse (right). Roof of cranium and brain are removed. Control pituitary weighed 1.8 mg.: it is the small squarish structure in the midline behind the optic nerve. Experimental pituitary weighed 174 mg., and was obtained 11 months after a dose of 200 μc of I^{131}.

length of which is an inverse function of the dose, in which pyknotic and necrotic tissues are gradually removed by invading leucocytes and macrophages, and replaced by fibrous tissue. Surviving cells and follicles present a strangely heterogeneous picture. A few follicles appear essentially normal. In some, both nuclei and cytoplasm are shrunken and seemingly moribund. In others the nuclei are pyknotic, while the cytoplasm appears to be in a state of very excessive activity—the cell is increased to more than three times its normal dimension and contains numerous droplets of colloid-like material. This condition has been called by some "colloid de-

generation." The colloid itself is highly vacuolated in such follicles. In mice given the minimum thyroid-lethal dose there are still surviving follicles in the isthmus and the cranial apex of the gland three weeks after treatment. Even these are gone after six weeks.

Properties of thyroid remnants which survive I^{131} treatment

Intrathyroidal doses of 2 microcuries per milligram of thyroid, as a rule, permit survival of a few thyroid follicles. Doses of 1 microcurie/milligram or less leave few, if any, signs of permanent damage. We have examined a large series of thyroid remnants which survived 2 microcuries/milligram dosages. At three months when, presumably, acute changes have subsided, small clumps of atypical follicles or afollicular cell groups may be found embedded in the fibrous scar, especially at its edge. The constituent cells have the appearance of "colloid degeneration" since most of them are swollen; the chromatin in their nuclei is clumped; their size is extremely variable; they contain large colloid-like droplets. We have examined such surviving bits of thyroid for periods up to one and one-half years after treatment and their structure appears to be substantially the same (Figs. 7, 8).

Neoplastic growth, or even metaplastic replacement, has not been observed. On the other hand it seems quite obvious, in mice at least, that the surviving thyroidal remnants are incapable of regeneration.

The state of function of the residual thyroid tissue has been of interest. When tracer doses of I^{131} are given mice with damaged thyroids of this type, it is found that they store less than 1 per cent as much iodine intrathyroidally as do normal mice. Unfortunately, it is impossible to estimate in terms of mass what fraction of a normal thyroid gland remains in the treated mice. Radioautographs of surviving thyroid have been prepared. They have indicated uniformly 1) that iodine uptake is slight, though demonstrable, and 2) the iodine which is taken up is localized in the colloid as in normal glands. It would appear, therefore, that when some thyroid tissue weathers a radiotoxic dose of I^{131} it may be so affected that it cannot regenerate, nor can it function to a normal degree.

EXPLANATION OF PLATE I

FIG. 5. Amorphous "ghost" thyroid follicles 3 days after a 1000 μc dose of I^{131}. Note edema and denuded tracheal epithelium. ×90.

FIG. 6. Complete absence of thyroid 270 days after 200 μc dose. Metaplastic tracheal epithelium. Hyalinized hypertrophy of perichondrium. ×90.

FIG. 7. Remnant of thyroid in cranial apex of gland 204 days after 100 μc dose. Gland replaced by fibrous mass. ×90.

FIG. 8. Detail of thyroid tissue which survived 100 μc dose. ×190.

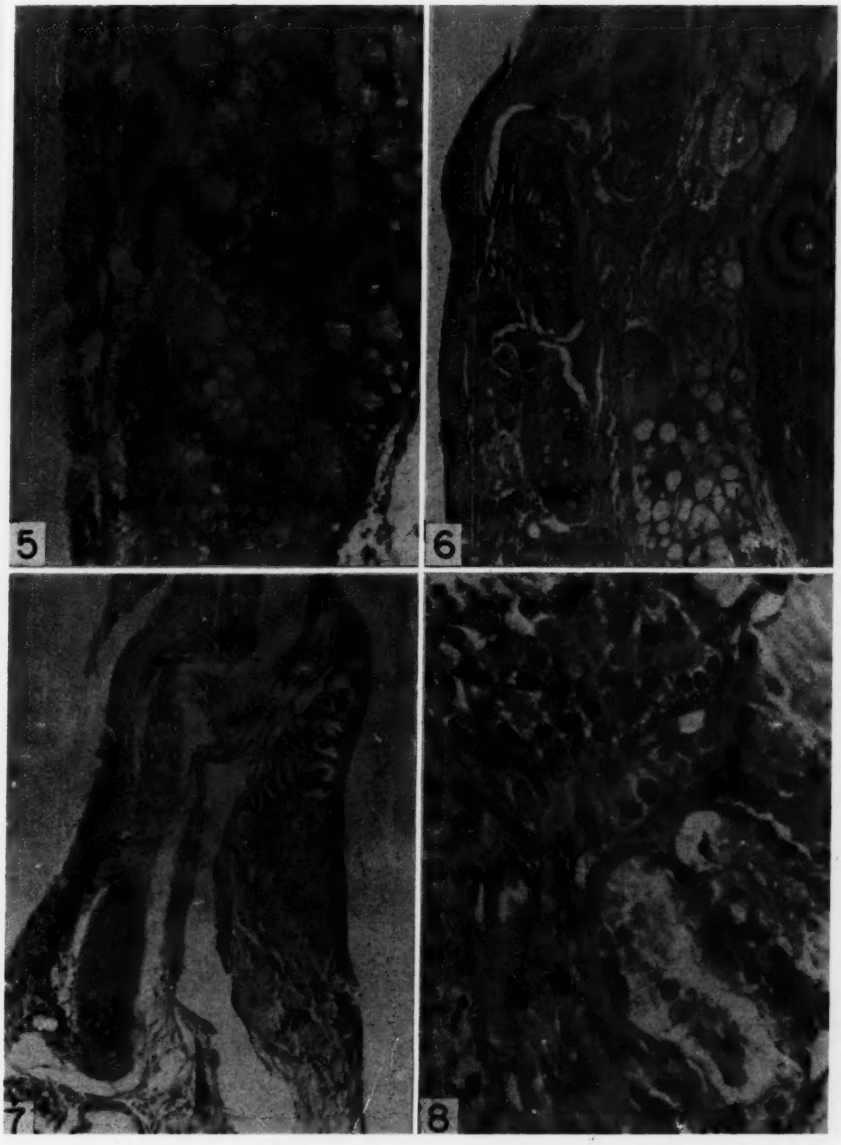

PLATE I

Function in I^{131} irradiated thyroids

In order to determine the physical dose, in equivalent roentgens, received by the thyroid it is important to know not only the maximum up-

take of I^{131} but also its rate of discharge. In making these determinations several interesting facts have been obtained incidentally. Figure 1 shows the rate of loss of accumulated radioactivity from thyroids of mice on Purina Chow diet. If all of the accumulated I^{131} were retained, this rate of the loss would be equal to the physical half-life of I^{131} (it would be halved every eight days). Various physiologic factors combine to increase the rate of loss of radioactivity and the overall rate of loss from the thyroid is referred to as the "biologic half-life." For presumably noninjurious doses in normal adult mice the biologic half-life is barely more than two days. For slightly more than thyroid-lethal doses (200 microcuries whole body; 4 microcuries/milligram of thyroid) the thyroidal biologic half-life is 1.25 days. For higher doses the loss of radioactivity is slowed again to a biologic half-life of two days. One interpretation is that a 4 microcuries/milligram thyroidal dose induces a loss of stored iodine into the blood from dead or injured follicles. Higher doses not only kill thyroid but also, as seen in histologic examination, injure blood vessels, and might interfere with resorption of hormonal radioiodine from the follicles. This would, of course, give the isotope a longer biologic half-life in the thyroid.

Skanse (10) and Feller *et al.* (9) have investigated other properties of radiation-injured thyroids. They have noted a decreased ability of exposed thyroids to store new iodine, to retain stored iodine, and to respond to goitrogenic or thyrotropic agents. Feller *et al.* (9), furthermore, have demonstrated a rise in plasma protein iodine, which is correlated with a loss of organic iodine from radiation-injured thyroids (doses of about 7.5 and 22 microcuries per milligram of rat thyroid). Similar rises in plasma iodine have been noted in humans subsequent to I^{131} therapy (Riggs (11)).

INJURIES TO THYROID-ADJACENT STRUCTURES

In the mouse the thyroid gland touches, and in some cases actually surrounds, the following organs and structures: two parathyroid glands, occasional thymic lobules, the trachea, the esophagus, the recurrent laryngeal nerve, and several muscles. Because of the small size of all these thyroidal

---

EXPLANATION OF PLATE II

FIG. 9. Fibrous ring-shaped growth almost occluding tracheal lumen. Denuded and metaplastic epithelium 155 days after 200 μc dose of I^{131}. ×90.

FIG. 10. Cross section of recurrent nerve. Variability in diameter of axis cylinders. ×190.

FIG. 11. Edge of thyroid and esophagus with skeletal muscle in between, 8 days after 200 μc dose. Necrosis of thyroid. Leucocytic infiltration and edema of perithyroidal tissue. ×90.

FIG. 12. Edge of pituitary tumor. Large chromophobic area. Some regions highly vacuolated. ×90.

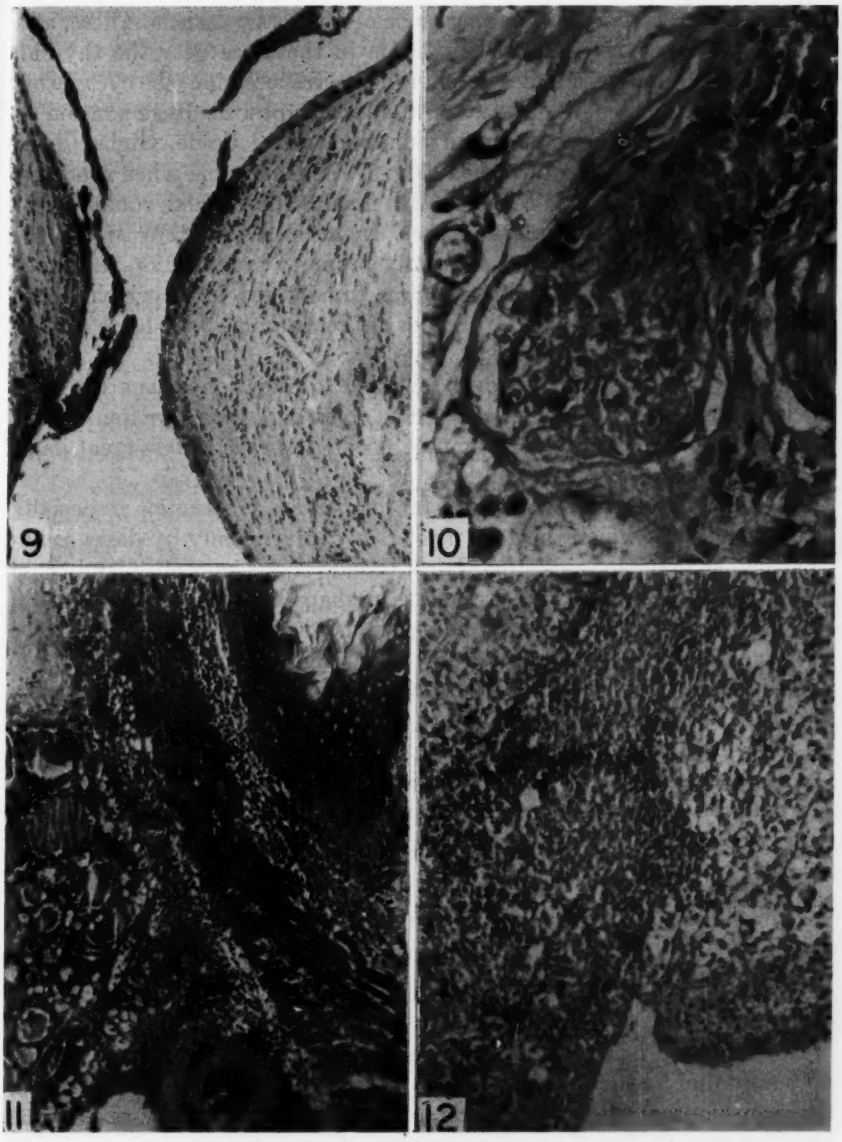

PLATE II

neighbors in the mouse, they all come wholly or partly within its aura of β-radiation after it has trapped I^{131}. Of the members of this group the most sensitive to radiation is the tracheal epithelium. Even less than thyroid-

lethal amounts of I^{131} lead to appearance of temporary lesions. These, as a rule, involve only the ciliated epithelium in the areas near the thyroid. Loss of cilia, pyknosis, and death follow in rapid succession, the cycle being completed within a few days after radiation exposure. Regeneration of normal epithelium occurs from surrounding normal tissue. Higher doses often denude large areas of trachea (Fig. 5). Regeneration, when it occurs, is not usually with normal cells but with unciliated cuboidal, squamous or stratified squamous metaplastic types. In mice of the CFW strain the tracheal tunica propria seems especially prone to proliferation. In about 5 per cent of this strain nodular fibrous tumors developed which partly occluded the tracheal lumen. A number of these tumors were large enough to kill their hosts (Fig. 9).

Another structure which proves sensitive to radiation emanating from the thyroid is the thymus. Lobules of this organ commonly are found near, or attached to, the thyroid. Thymus so located always suffers great damage, even from relatively small doses of I^{131}.

Parathyroid glands are fairly resistant to radiant destruction, especially in CFW mice, in which they are irreversibly injured only by doses somewhat higher than thyroid-lethal. Parathyroids of A-strain mice, and those of some C_{57} mice, are more susceptible, perhaps because of differences in the vulnerability of their vascular supply, and often are fatally affected by less than thyroid-lethal doses.

Aside from being included in the zone of the brief but extensive perithyroidal edema reaction, the juxtathyroidal muscles and esophagus seem to suffer no ill effects (Fig. 11).

In mice with initial I^{131} doses higher than 4 microcuries/milligram of thyroid, the recurrent nerve is affected. Neurilemma and sheath cells undergo pyknosis, and many appear to be lost. Axis cylinders become very irregular in diameter (Fig. 10).

GENERAL AND METABOLIC EFFECTS

Younger animals given thyroid-killing doses of I^{131} grow more slowly than normal mice and reach a plateau at about 80 per cent of normal body weight (Fig. 2).

Reproduction is virtually halted. More than 300 treated females bore only a total of 5 litters during the first post-treatment month, and 4 litters between months 2 to 5. Histologic examination of the ovary reveals the basis for this sterility. There is a complete absence of ova in most animals. The pathologic picture is the same as that described by Brambell and Parkes (12) in mice given high doses of X-ray, and the description will not be repeated here. The male reproductive system, strangely enough, appears to be entirely unaffected.

Oxygen consumption is depressed for the first month or two after I^{131}

radiation exposure. Thereafter it rises and may even exceed normal (Fig. 3). In order to provide another basis on which to judge hypothyroidism, 20 radioiodine-treated mice were placed in a 5° C. refrigerator. In six hours all but 1 were dead, while controls appeared quite unharmed by such treatment.

Acute histopathologic changes were seen in the kidney (glomerulonephritis) and liver (periportal cirrhosis). Only the liver injury left permanent fibrous scars.

PITUITARY TUMOR

About eight months after thyroid-lethal doses of I^{131}, or doses small enough to leave thyroid remnants, more than 90 per cent of treated mice develop a non-invasive chromophobic tumor of the anterior pituitary (Fig. 12). The tumor can become more than half as large as the brain (Fig. 4), and it seems limited in its growth only by the fact that pressure on the brain soon induces blindness, locomotor abnormalities and, finally, death. The etiology of this growth is obscure at the present time. That it is the product of some definite physiologic mechanism seems implied by its high incidence.

We have tried to test the hypothesis that the pituitary possibly accumulates sufficient radioiodine to exceed some relatively low threshold of radiosensitivity. In the presence of high background radiation in blood of animals given radiotoxic doses of I^{131} our results were inconclusive. It should be noted, however, that Courrier *et al.* (13) found that I^{131}-labelled thyroxine accumulates in the pituitary to some extent. In 1 human that came to autopsy soon after a large dose of I^{131}, Chapman (14) found 3 per cent of the administered isotope in the pituitary. In this instance the pituitary was second only to the thyroid in its content of I^{131}.

Spontaneous hypophyseal tumors in mice are extremely rare, but chromophobic tumors are easily obtained experimentally in response to chronic estrogenization. Some of our mice, especially those of the C_{57} strain, had extremely long periods of vaginal cornification, and presented other evidence of continued high levels of circulation estrogen (hardening of bones, enlarged mammary glands and uterus, loosened pubic symphysis). On the other hand, pituitary tumors of equal frequency were found in males, and in permanently diestrous females. Despite this inconsistency, 60 radioiodine-treated mice were gonadectomized. These have been yielding pituitary tumors as readily as intact animals.

RECAPITULATION AND DISCUSSION

Against the background of experience with dosage effects in experimental animals, it is interesting to reconsider the quantities of radiation reported by several workers as useful in management of hyperthyroidism. The thyroid-lethal radiation dose for mice is about 120,000 e.r. Under

stated circumstances a dose of 50,000 e.r., which leaves bits of surviving thyroid, also produces such undesirable side effects as injury of parathyroids, recurrent nerve, and trachea, sterilization of the ovary, and pituitary tumors. Similar partial thyroidal destruction has been reported in the rat after intrathyroidal doses of only 20,000 e.r. (Findlay and LeBlond, (15)). Because of the size of the mouse thyroid and the escape from it of much of the β-radiation from entrapped I^{131}, the intrathyroidal dose may have been as little as 25,000–30,000 e.r. Werner, Quimby and Schmidt (7) have estimated that in their own successful use of I^{131} for treatment of hyperthyroid patients, and in the work of others, the intrathyroidal dose is about 5,000–6,000 e.r.

What of the radiation hazard to thyroid-neighboring organs? It is generally considered that the thickness of the thyroidal capsule in humans will absorb and dissipate most of the β-radiant energy. That the I^{131} radiation (possibly the gamma component) may induce tracheal damage in man has been reported by Werner *et al.* (7). Lukens (16) has discussed the tracheal injuries found after therapeutic x-irradiation of thyroid. The possibility that tracheal tumorous growths, such as those found in our mice, may be induced must be borne in mind during the post-treatment observation of I^{131}-treated individuals.

Ovarian sterilization by I^{131} probably should be adjudged a potential hazard only under circumstances in which thyroidal iodine uptake is less than 10 per cent. In building up intrathyroidal doses of radiation for glands of such meager iodine appetite, the blood and body fluid levels of I^{131} often will become high enough to be sterilizing or at least very likely mutation-inducing. There is a corresponding danger, if not frank injury, to other radiation-sensitive peripheral tissues.

The appearance of pituitary tumors in mice after even less than thyroid-lethal doses of I^{131} introduces a most unexpected complication. The high incidence of this fatal growth indicates that it is the product of a definite physiologic mechanism. It is possible that the tumorous reaction represents a functional peculiarity of the mouse. Until this mechanism can be identified, however, it will continue to present a most interesting and challenging problem.

In summary, undesirable sequelae to high doses of I^{131} which have been found in mice include: 1) curtailment of growth, 2) failure of functional and regenerative properties in the thyroid surviving less than thyroid-lethal doses, 3) parathyroid injury, 4) tracheal injury and tumors, 5) recurrent nerve injury, 6) ovarian sterilization, and 7) fatal adenohypophyseal tumors. The dosage level from which most of these changes occur in mice, depending on the criteria consulted, are as much as twenty times greater or as little as four times greater than the doses given humans for therapy of hyperthyroidism. Some of the sequelae may be peculiar to mice, as well

as to the dosage levels used. Some of them almost certainly are. The remainder are serious enough to require further inquiry concerning their significance or possible roles in radiation therapy of human thyroids. In an excellent review of their own experience with therapy of hyperthyroidism Pemberton, Haines and Keating (4) have recommended that use of I^{131}, at the present time, be restricted to aged or inoperable individuals. When the malady treated is not a fatal one, and unless there are no alternative methods of treatment available, it does not yet seem worth while to accept the risks implicit in the use of this powerful agent.

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THE RESPONSE OF THE THYROID GLAND TO THYROTROPIC HORMONE AS AN AID IN THE DIFFERENTIAL DIAGNOSIS OF PRIMARY AND SECONDARY HYPOTHYROIDISM*†

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THE differentiation of hypothyroidism of pituitary origin from that due to primary impairment of the thyroid gland may be very difficult. Proper treatment is dependent upon correct distinction of the two conditions. The problem is met whenever hypometabolism is encountered along with evidence of diminished function of other endocrine glands, such as the adrenal cortex or the gonads. One must first decide whether the hypometabolism is a result of hypothyroidism; for in many conditions, such as anorexia nervosa, severe hypometabolism may exist when there is ample laboratory evidence of a normally functioning thyroid gland.

The usual laboratory data on thyroid function do not suffice to distinguish between primary thyroid failure and pituitary failure. The trends are the same in both, and elevated serum cholesterol and axillary hair loss also may prevail in both. Diminished function of other target glands of the pituitary favors a diagnosis of hypothyroidism of pituitary origin. However, there may be diminished function of these glands in primary myxedema also (1): for instance, in a thyroidectomized rat the weight of the adrenal glands diminishes and the cortex shows changes in cellular pattern compatible with hypofunction. The clinical situation is further complicated by the existence of a bi-glandular disease (thyroid fibrosis accompanied by adrenal atrophy) recently observed by one of us (2). Thus, there are three conditions in which hypothyroidism is a feature of pluriglandular disease: i) pituitary insufficiency, ii) severe hypothyroidism causing hypoadrenocorticism, and iii) bi-glandular disease of the thyroid and adrenal glands with a normal pituitary gland.

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** Professor of Medicine, Leiden University, Leiden, Holland. Rockefeller Travelling Fellow, 1949–1950.

This article will be included in the bound volume of the "Transactions of the American Goiter Association," published by Charles C Thomas, Publisher, which will be available for sale early in 1951.

It seemed reasonable to attempt a differentiation of these conditions by testing the responsiveness of the thyroid gland to thyrotropic hormone. This was based on the consideration that hypothyroidism arising from atrophy of the thyroid gland secondary to hypopituitarism should respond to thyrotropin, whereas the fibrotic thyroid of primary myxedema should not. It was borne in mind however that atrophy from pituitary failure of long standing might lead to unresponsiveness, probably through fibrotic changes as described by Sheehan (3), and as we also have observed.

METHODS

Previous investigators, using more or less crude pituitary extracts, measured the response of the thyroid gland with relatively unspecific indices which were not necessarily directly related to thyroid function. Sharpey Schafer and Schrire (4) used, along with basal metabolic rates and creatine excretion, the palpable enlargement of the thyroid gland. Thompson and his associates (5) relied primarily on the basal metabolic rate as an index of response.

In this study it was our endeavor to obtain objective data on the functional status of the thyroid gland. Before and after stimulation with thyrotropic hormone (TSH)[1] the following procedures were carried out: serum protein-bound iodine (PBI) determinations, accumulation rate of radioactive iodine (I^{131}) tracer doses in the neck, total I^{131} uptake after forty-eight hours by in vivo measurement and total 48-hour excretion of I^{131} in the urine. Basal metabolic rates (BMR) were taken several times.

The lyophilized thyrotropic hormone preparation was dissolved in sterile saline and injected subcutaneously twice daily in 12.5-milligram doses. The serum protein-bound iodine determinations were made by a modification of the method of Barker (6). Tracer amounts of I^{131} were given to the fasting patients in doses of 40 to 100 microcuries, with 10 micrograms of added potassium iodide as carrier. Counting over the neck was done at a short distance with a platinum cathode Geiger-Mueller tube which was heavily shielded. The in vivo uptake by the thyroid gland was determined by the method of Skanse (7). Accumulation rates of I^{131} in the thyroid gland were plotted according to the method of Stanley and Astwood (8), although no attempt was made to calculate gradient values. When the second tracer dose (after TSH treatment) was given, the preceding 24-hour urine speci-

[1] The thyrotropic hormone preparation was made available through the courtesy of Dr. John R. Mote of Armour and Co., Chicago, Ill. Each vial contained 25 mg. of Lot H 71608 purified thyrotropic hormone of 4.5 Evans units per mg. Adrenocorticotropin was present on a weight basis 10 per cent of La-I-A. Gonadotropins were practically absent, and growth hormone, oxytocic and pressor substances, and prolactin were very low.

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TABLE 1

Case No.	Unit No.	Final diagnosis	*Before TSH*				Other treatment during TSH administration	Days on TSH	*After TSH*				Change in accumulation rate
			BMR %	PBI, micrograms %	Radioactive iodine				BMR %	PBI, micrograms %	Radioactive iodine		
					48-hour uptake by thyroid	48-hour urinary excretion					48-hour uptake by thyroid	48-hour urinary excretion	
1	635804	Hypometabolism	−31 −23	4.0	31%	—	None	3	−13 −11	7.6	60%	—	Distinct increase
2	672203	Primary myxedema	−41 −44	0.9	14%	—	None	3	−45 −41	0.9	13%	93%	No change
3	583121	Primary myxedema	−37 −41	0.5	3%	91%	None	6	−47 −40	0.2	3%	85%	No change
4	543385	Primary myxedema	−31 −31	3.5	9%	90%	Thyroid U.S.P., 60 mg. daily	9	−22 −29	3.5	8.5%	87%	No change
5	568954	Primary myxedema	+ 1 − 7	5.5	3.8%	85%	Thyroid U.S.P., 100 mg. daily	6	− 2 − 4	3.1	9.7%	80%	No change
6	614303	Hypopituitarism	−15	2.5	5%	57%	Thyroid U.S.P., 60 mg. daily	8	−15 − 8	7.2	33%	63%	Very distinct increase
7	396128	Hypopituitarism	−37 −32	3.7	36%	65%	Thyroid U.S.P., 30 mg. daily	6	−23 − 4	13.7	82%	24%	Very distinct increase
8	12728	Primary myxedema*	−18 −28	—	—	—	None	3	−22 −24	—	—	—	No change
9	603857	Primary myxedema	−35 −24	1.6	14%	—	None	6	−26 −35	9.2	25%	—	Distinct increase

* A preliminary study. Gradient studies were the only ones done with I^{131}. No appreciable quantity of I^{131} accumulated in the thyroid gland either before or after the administration of TSH. Armour thyrotropin Lot #G. 59803 was used for this patient only.

men was collected in order to enable approximate correction for the 48-hour urine specimen following the second tracer dose. The in vivo uptake after the second tracer was calculated by subtracting the portion of I^{131} of the first dose still present in the gland before the administration of the second dose.

Four of the patients (Cases 4, 5, 6 and 7) were receiving desiccated thyroid in the dosage shown in Table 1. This medication was not withdrawn, since there is no reason to expect that the thyroid gland is less responsive to TSH stimulation during the administration of thyroid (9). Withdrawal on the other hand might have made the interpretation of results more difficult.

RESULTS

Nine patients with hypometabolism were studied. Six of these were given a diagnosis of primary myxedema and 2 were considered to have hypopituitarism. The remaining patient apparently had a normally functioning thyroid gland and a low basal metabolic rate. The results of the studies are arranged in Table 1. The data on Cases 1, 3, 6 and 7 are charted in Figures 1, 2, 3 and 4. The case histories are summarized in the appendix.

Case 1 (Fig. 1) was that of a woman with a variety of vague complaints and excessive fatigue who had hypometabolism without any signs of myxedema. She showed a clear response after a three-day course of TSH injections. Both the increase of the PBI and the in vivo uptake of I^{131} were more distinct than the rise in BMR. The patient may be considered as a control case for the activity of the particular lot of TSH used in this study. Her serum cholesterol level was 309 milligrams per cent. No explanation for this was found.

Although initially TSH was given for only three days, it was soon apparent that this period might be inadequate in a long-dormant gland. Accordingly, in Cases 3 through 9, the TSH was given for six or more days. It is of interest that in the patients who responded to TSH (Cases 1, 6, 7 and 9) the changes in PBI and I^{131} uptake are far more pronounced than are those of the BMR values. These indices are not only more specific for evaluation of thyroid function than BMR values, but also seem to be more sensitive.

DISCUSSION

The validity of a method which uses the response of the thyroid gland to TSH stimulation for differentiating between primary and secondary hypothyroidism rests on at least two assumptions: 1) that thyroid glands in patients with primary hypothyroidism *do not react* to TSH, *i.e.*, possess no functioning tissue, and 2) that patients suffering from hypopituitarism

respond to TSH stimulation. Neither of these assumptions is necessarily correct. In Case 2, for instance, a patient with classic myxedema, we obtained data after TSH stimulation which indicated that there was functioning tissue left. Thus, although neither BMR, PBI, nor in vivo I^{131} uptake data changed after TSH treatment, there was a slight discrepancy between the times maximum counts were reached over the thyroid and the thigh. Maximum counts were reached in two hours over the thyroid and in thirty to sixty minutes over the thigh. This is best explained on the basis of functioning tissue left in the thyroid gland.

The patient in Case 9 also presented the classic findings of primary athyreotic myxedema. Pituitary hypofunction was ruled out by a normal insulin tolerance curve, high excretion of follicle-stimulating hormone in the urine and a low-normal 17-ketosteroid excretion. Yet after TSH administration there was a rise in the protein-bound iodine of her serum. This result is explicable if one assumes that there was a failure of TSH production without concomitant failure of production of other tropic hormones of the pituitary. A more probable explanation is that the destructive process in her thyroid gland had not completely destroyed the gland. It seems quite possible therefore that remnants of thyroid tissue may lead to confusing results.

It has already been mentioned that a dormant thyroid gland unstimulated by TSH might in time become fibrotic and therefore unresponsive to exogenous TSH (3). Previous to the studies reported here we endeavored to stimulate the thyroid gland of a patient with the classic history and findings of Sheehan's disease of fifteen years' duration. Even after nine days of TSH administration there was no significant rise in the PBI and the BMR had risen only slightly. Perhaps a longer period of stimulus would eventually have restored the gland to a normally functioning state.

Of the 9 cases reported here, 3 showed a striking change in the indices of thyroid function after TSH, 5 failed to show any noteworthy change and 1 showed moderate changes. These results were generally consistent with the clinical diagnostic impressions.

This test has value only because of the great difficulty which may exist in making a clear differentiation between primary and pituitary myxedema on any other basis at present. Properly interpreted, it may prove helpful. Much more experience is needed before it will be possible to evaluate the significance and the limitations of the test.

SUMMARY

1. Thyrotropic hormone was given to a series of 9 patients with hypometabolism. One of these, except for an elevated serum cholesterol concentration, was otherwise normal; 6 were considered to have primary

myxedema; and 2 were given a final diagnosis of hypopituitarism. Thyroid gland function was assessed by determinations of basal metabolic rate, the serum protein-bound iodine, and by radioiodine studies.

2. Following administration of thyrotropic hormone there was a rise in the indices of thyroid function in the patient with nonthyroidal hypometabolism, in the 2 patients with hypopituitarism, and in 1 of the patients with primary myxedema. The last was interpreted as a response of remnants of functional thyroid tissue.

3. The results suggest that repeated injections of thyrotropic hormone may be an aid in the differential diagnosis of primary and secondary hypothyroidism.

4. The limitations of the text are discussed.

Acknowledgment

The authors would like to acknowledge their indebtedness to Dr. Fuller Albright for making available much of the auxiliary endocrinologic data obtained on these patients.

CASE REPORTS

Case 1. N. M., MGH Unit #635804, a 50-year-old housewife complained of easy fatiguability and constipation. Two years previously she had undergone a hysterectomy for carcinoma of the cervix. She deemed depressed but physical examination offered no explanation for her complaints. Determinations of the basal metabolic rate were minus 31 and minus 23 per cent. The serum cholesterol was 309 milligrams per cent. Laboratory data relative to her thyroid status are given in Table 1 and Figure 1. *Final diagnosis:* Hypometabolism.

Case 2. A. S., MGH Unit #672203, a 17-year-old school girl, had always been slow in school. Menarche was at 13 years of age. Her periods were irregular and menstrual flow was excessive. She was sensitive to cold and was constipated. On examination, she had a typical myxedematous appearance, with thickened skin. The thyroid was barely palpable on the left side. Basal metabolic rates were minus 41 and minus 44 per cent. A serum cholesterol was 525 milligrams per cent. An insulin tolerance test gave normal results. Subsequently, she made an entirely satisfactory response to thyroid therapy. *Final diagnosis:* Primary myxedema.

Case 3. A. S., MGH Unit #583121, a 68-year-old woman, entered the menopause gradually at age 40 without hot flashes. Her last pregnancy occurred four years earlier without hemorrhage or other complications at parturition. For years she had been sensitive to cold and for five years had noticed loss of hair on her scalp and in her axillae. A BMR was minus 40 per cent and a serum cholesterol was 207 milligrams per cent. There was some doubt as to whether she was suffering from primary or secondary myxedema. The following endocrine data were obtained: normal insulin tolerance curve, absence of 17-ketosteroids in the urine, gonadotropins in urine positive for 192 mouse units per 24 hours (consistent with the menopause). *Final diagnosis:* Primary myxedema (Fig. 2).

Case 4. M. C., MGH Unit #543385. This 54-year-old housewife was first seen in 1948 because of blurring of vision. Temporal visual field defects were found. X-ray examination of the sella turcica showed displacement of clinoids. Her BMR was minus 34 per cent. The diagnoses of pituitary chromophobe adenoma and pituitary myxedema were

proposed. Consistent with these was the absence of gonadotropins in the urine (FSH negative for 6.5 mouse units per 24 hours). However, there was normal responsiveness to hypoglycemia after insulin, normal axillary and pubic hair, and urinary 17-ketosteroids of 2.4 milligrams per 24 hours. She received x-radiation to the sella turcica and thyroid medication. The gonadotropins in the urine became positive for 13 and 26 mouse units per 24 hours. Her clinical condition improved markedly. She did not

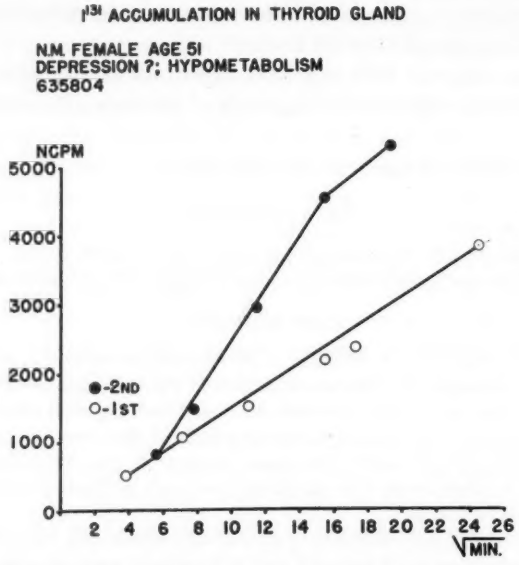

FIG. 1. Patient N. M., Case 1. Accumulation gradients of I^{131}. Ordinate: net counts per minute over the neck. Abscissa: square root of time in minutes. Tracer dose of I^{131} given at zero time. Open circles are net counts per minutes before TSH: closed circles, after TSH.

respond to TSH injections. The final tentative diagnoses were pituitary chromophobe adenoma and primary myxedema.

Case 5. M. H., MGH Unit #568954, a 59-year-old clerk, was first seen two years earlier because of loss of energy for seven years and dry hair for five years. Menses had ceased twelve years earlier without hot flashes. She presented a typical myxedematous appearance. There was absence of axillary hair, a BMR was minus 30 per cent, a PBI was 1 microgram per cent and 17-ketosteroids were 1.6 milligrams per 24 hours. The titer of urinary gonadotropins was positive for 6.5 but negative for 13 mouse units per 24 hours. The blood sugar showed a 50 per cent drop after 45 minutes and did not spontaneously return to the fasting level in 120 minutes. Serum sodium was 108 milliequivalents per liter. A diagnosis of panhypopituitarism was made and she was treated with 30–60 milligrams of desiccated thyroid daily and extra salt. She did extremely well. At the time of the present admission the following were found: there was a 63 per cent drop in the circulating blood eosinophils after an injection of epinephrine, an insulin tolerance test showed her not to be insulin sensitive, the excretion of 17-ketosteroids and

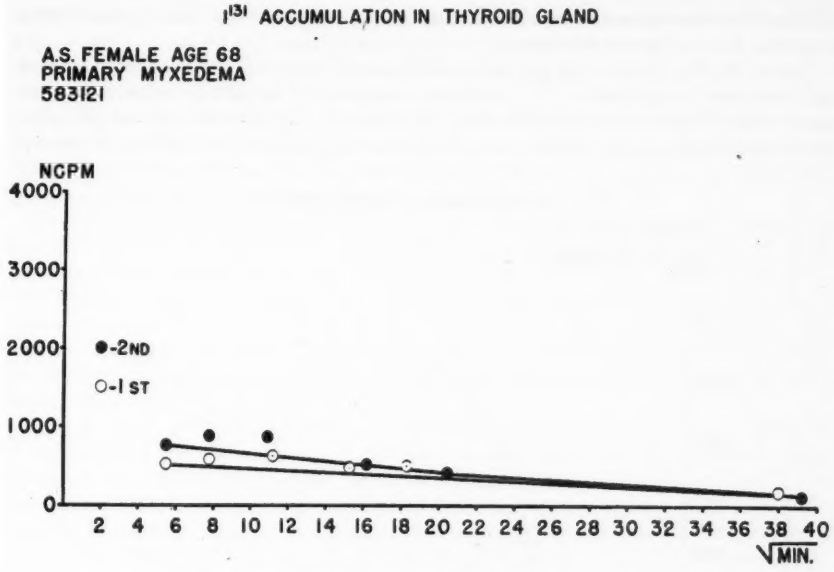

FIG. 2. Patient A. S., Case 3. Accumulation gradients of I^{131}. Symbols are as in Figure 1.

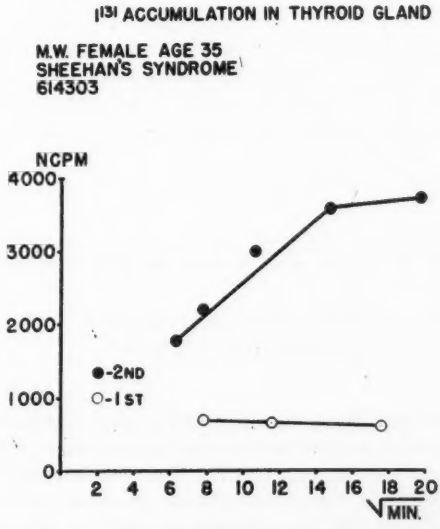

FIG. 3. Patient M. W., Case 6. Accumulation gradients of I^{131}. Symbols are as in Figure 1.

of 11-oxysteroids was low, and a Wilder test gave positive results. The final tentative diagnosis was primary myxedema.

Case 6. M. W., MGH Unit #614303, a 35-year-old housewife developed amenorrhea and weakness immediately after a delivery complicated by severe hemorrhage five years earlier. There was failure of axillary hair growth. The thyroid was not palpable. There were no signs of myxedema, but a BMR was minus 38 per cent and the cholesterol

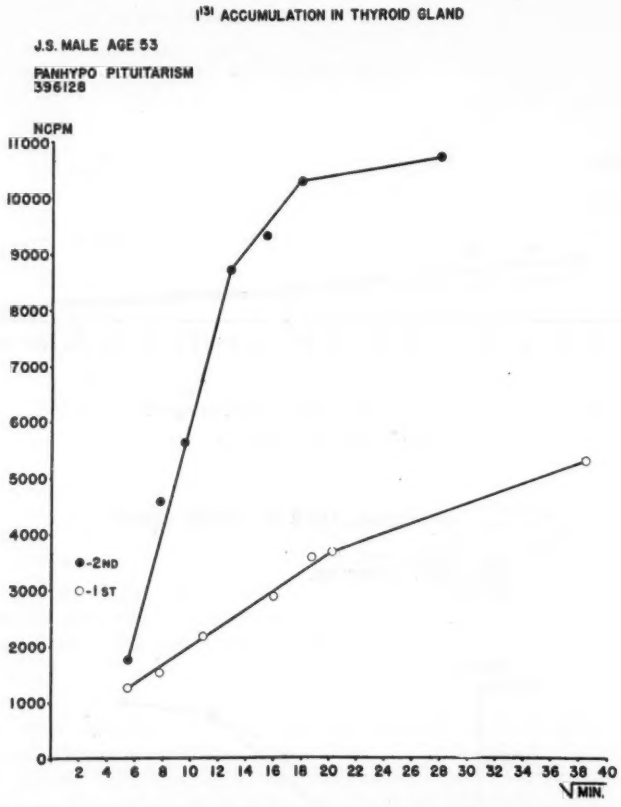

FIG. 4. Patient J. S., Case 7. Accumulation gradients of I^{121}. Symbols are as in Figure 1.

was 358 milligrams per cent. There were no gonadotropins in the urine at 6 mouse units per 24 hours. An insulin tolerance test showed hypoglycemia unresponsiveness. The results of the Wilder test were strongly positive. The 17-ketosteroids were 1.6 milligrams per 24 hours. *Final diagnosis:* Panhypopituitarism (Sheehan's syndrome) (Fig. 3).

Case 7. J. S., MGH Unit #396128, a 53-year-old male has been described extensively (10) as a case of hypopituitarism following head injury. At the age of 15 a bullet entered his left orbit and passed through the sella turcica, probably destroying hypophyseal

tissue. The physical appearance of the patient was that of hypopituitarism. His BMR was between minus 30 and minus 40 per cent at age 46, and the PBI was 3.8 gamma per cent (low-normal). Six years later, BMR values again ranged between minus 30 and minus 40 per cent, but the patient was taking 30 milligrams of thyroid U.S.P. daily. The in vivo uptake of an I^{131} tracer dose was 36 per cent and the 48-hour excretion was 65 per cent. This patient reacted strongly to a six-day course of TSH injections. Although it is clear that he had hypopituitarism, it should be stressed that he did not have hypothyroidism. *Diagnosis:* Partial hypopituitarism (Fig. 4).

Case 8. A. U., MGH Unit #12728, a 72-year-old housewife, had been treated for myxedema in this hospital for thirty-one years until a year previously, when her family physician discontinued the thyroid medication. The classic signs and symptoms of myxedema promptly developed. Her blood cholesterol concentration was 493 milligrams per cent. She was found not to be sensitive to insulin and a Wilder test gave normal results. She showed a high level of follicle-stimulating hormone in the urine. She made a prompt response to the administration of 0.1 gram of desiccated thyroid daily. *Final diagnosis:* Primary myxedema.

Case 9. M. B., MGH Unit #603857, a 54-year-old spinster, was admitted for treatment of carcinoma of the endometrium. Myxedema was an incidental finding and the blood cholesterol was 273 milligrams per cent. She was not insulin sensitive and there was a high level of follicle-stimulating hormone in the urine. There was a normal fall in circulating eosinophils after an injection of epinephrine. She made a dramatic response to the administration of desiccated thyroid. *Final diagnosis:* Primary myxedema.

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PRESENT CONCEPTS OF THE PATHOLOGIC PHYSIOLOGY OF EXOPHTHALMOS*†

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IN 1934 the Journal of the American Medical Association published an editorial (1) which reprimanded an English author who had referred to the problem of the mechanism of exophthalmos as still little understood. The article went on to say that exophthalmos was caused by sympathetic stimulation and that it was unfortunate that knowledge about it had been poorly disseminated. In spite of the feelings of the author of that editorial sixteen years ago, the etiology and pathologic physiology of exophthalmos remain an outstanding and puzzling problem in the field of thyroid disease.

The purpose of this presentation is to review some of the theories of the mechanism of progressive exophthalmos and to bring together certain clinical, anatomic, and pathologic facts which should direct us toward a future understanding of this mechanism. The theories are considered in the light of their current acceptability. Physical signs pertaining to the eyes are analyzed. Anatomic relationships within the orbit are illustrated. Pathologic findings in the orbit are compared to such findings produced experimentally with thyroid-stimulating hormone (TSH). Hormonal relationships are discussed. Data from a review of all cases in the world literature are introduced. The facts assembled are used to support what seems to be the most likely mechanism of progressive exophthalmos.

THEORIES OF EXOPHTHALMOS

The idea that overactivity of the cervical sympathetics causes exophthalmos apparently took its origin from the work of Claude Bernard (2) who, in 1852, observed that electrical stimulation of the cervical sympathetics in animals caused widening of the palpebral fissures, dilatation of

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the pupils and exophthalmos. The theory gained support from many authors but there were differences in opinion regarding the mode of action of the sympathetics. Then the smooth muscle of Müller (3) in the orbit of animals came into the picture. Later MacCallum and Cornell (4) and Code and Essex (5) observed that this muscle contracted and squeezed the globe forward. Thus, the removal of the cervical sympathetic trunks as a surgical treatment for exophthalmos and Graves' disease was popularized by Jaboulay (6), Jonnesco (7) and C. H. Mayo (8). Although Balacescu (9) reported very successful results in his review of the literature in 1902, the procedure fell into disuse. It has subsequently been shown by Harling (10), Landström (11), Whitnall (12), and Russell (13) that Müller's muscle is only vestigial in man. It has also been shown that stimulation of the cervical sympathetics in man causes little if any protrusion of the globes (4) (14) (15).

It was next pointed out by Landström (11) that smooth muscle fibers (Landström's muscle) extending from the rim of the orbit to the equator of the globe might pull the globe forward, but it seems unreasonable that this muscle could pull the globe out beyond its own attachment. Krauss (16) and Fründ (17) tried in still another way to link the sympathetic nerves to exophthalmos by postulating venous distention caused by the contraction of smooth muscle fibers lying around the ophthalmic veins in the posterior part of the orbit. The fact that the exophthalmos, which they referred to, had disappeared at death indicated that it was not the malignant phase which we are concerned with in this discussion. In a review of 359 cases of severe exophthalmos in the world literature the engorgement of retinal veins was only occasionally mentioned, and when mentioned, was usually found in the most extreme cases. Other authors have blamed engorgement of retrobulbar vessels without incriminating the cervical sympathetics. Rundle's case (18) with an orbital varix gives an excellent example of the enormous pooling of blood that is necessary to produce severe proptosis. This, however, does not discredit the suggestion that chronic venous stasis may cause some edema.

A relaxation of the extra-ocular muscles has been another explanation of exophthalmos supported by many early authors. Wilson (19) after having found small degenerated extra-ocular muscles at postmortem examination in Graves' disease, postulated that such muscles were unable to counteract the normal outward thrust of retrobulbar tissues. Tilley (20) has suggested that retraction of the lids also removed a restraining force. Such a theory of relaxation of muscles seems untenable. The enormous pressure in retrobulbar tissue at the time of orbital decompression, the extrusion of tissue around the globe beneath the lids, and the continued extrusion of tissue from the orbit after enucleation, as described by Griffith (21), Moore (22),

O'Connor and Pierce (23) and Thomas and Woods (24), indicate that the lengthening of the muscles is probably secondary rather than primary.

There are several theories based on an increase in the volume of retrobulbar tissue, namely: increase in retrobulbar fat, increase in the size of extra-ocular muscles, or edema. The edema has been explained as an inflammatory reaction, obstruction to lymphatics or localized myxedema. Having narrowed down the field of theories to those which are based on an increase in retrobulbar tissues let us turn to some of the gross clinical observations which tell us something of what is going on.

CIRCUMSTANCES UNDER WHICH PROGRESSIVE EXOPHTHALMOS IS FOUND

Severe progressive exophthalmos appears in three clinical states. It is seen as a part of Graves' disease; it is seen perhaps more often after thyroidectomy when the picture of thyrotoxicosis has been ameliorated; and finally it is seen in patients who suffer from what Brain (25) (26) preferred to call "exophthalmic ophthalmoplegia," which is characterized by weakness of the extra-ocular muscles and exophthalmos but not accompanied by a goiter or thyrotoxicosis. These three clinical pictures and their numerous intermediate states do not all fit the picture described by Parry (27), Graves (28) or Von Basedow (29). To avoid criticism in the use of the term "Graves' disease" to cover all three states, perhaps it is fair to say that they are variations of a Graves' syndrome. Most persons will agree that they represent the same pattern, because with the time honored test of iodine administration, there is usually a decline in metabolism, whether it was originally elevated or normal. It thus seems fair to look upon these clinical states as basically the same phenomenon. Means (30) has coined the term "hyperophthalmopathic Graves' disease" to describe these patients with a major eye problem.

Unfortunately most of the recent writers have dwelt on the progressive exophthalmos which is associated with normal or subnormal basal metabolic rates. Many have implied and others have stated that so called malignant exophthalmos does not occur with the more severe degrees of hyperthyroidism. These authors have been intrigued by the unique paradox of exophthalmos and have thus been prompted to publish their observations. If one reviews all of the reported cases in the world literature and particularly those reported before the turn of the century (when the mortality from thyroid surgery restrained the enthusiasm of the surgeon) one finds that there were many patients in whom exophthalmos finally resulted in the loss of vision or of the eye while the symptoms of severe thyrotoxicosis were present.[1]

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[1] Von Graefe (31), from the literature to 1857, collected 14 patients with corneal

PHYSICAL EYE SIGNS ASSOCIATED WITH EXOPHTHALMOS

There has been an inclination to misconstrue the term "exophthalmos," which means protrusion of the globe. It has been a common failing among clinicians to be misled by the illusions that other eye signs create. Certain eye signs, when associated with true proptosis, are highly significant in the detection of impending malignant exophthalmos, whereas certain other signs merely create the illusion of which we should be aware.

Some time ago, the author reported (33) measurements taken with the Hertel exophthalmometer, of the prominence of the eyes in 233 patients before and following thyroidectomy. The study was prompted by the work of Soley (34) who found an increase of 1.5 mm. or more in the prominence of the eyes in 40 per cent of patients. The toxic patients whom we observed were prepared for surgery by iodine administration, so that many remained slightly toxic at the time of thyroidectomy. During the course of these repeated daily observations, many of the eye signs dramatically disappeared but simultaneously the true prominence of the eyes increased 1.25 mm. or more in 65.3 per cent of these patients subjected to thyroidectomy for Graves' disease. The lid retraction, stare, lid lag, and muscle tension about the eyes disappeared and contributed to the false impression of marked improvement in exophthalmos.

From this experience and observations on progressive exophthalmos, we may divide eye signs into two groups (Table 1): on one hand, those signs which are often associated with the stimulated phase of Graves' disease and which are not necessarily associated with exophthalmos; on the other hand, those signs which may be associated with true proptosis and which should warn the clinician of the possibility of a future eye problem.

From a limited experience with patients suffering from progressive (malignant) exophthalmos and from those described in the literature, it is possible briefly to analyze the development of symptoms and the ultimate courses that the disease may follow. The order of onset of the symptoms is variable. Increasing prominence of the eyes is usually accompanied by a fullness of the lids. A sense of irritation or pressure about the eyes is often associated with lacrimation. A watery swelling of the scleral conjunctiva and distention of the neighboring vessels begins at the lateral, and later at the medial canthus. The globular folds of edematous conjunctiva join below the limbus and spread to the conjunctival margin of the lower lid,

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ulceration occurring in severer cases of Graves' disease and 20 patients who had lost both eyes.

Sattler (32), found 74 cases in the literature to 1908; he looked upon corneal ulceration as occurring in the more severe cases of Graves' disease.

The author, in a recent survey of the world literature, found 21 additional cases.

thus tending to evert the lower lid and interfere with the normal lacrimal drainage.

EVIDENCE OF AN INCREASE IN RETROBULBAR TISSUE VOLUME

Certain characteristics of the bulging of the lids have rather obvious anatomic relationships as pointed out by Rundle and Wilson (35) (Fig. 1). Numerous observations indicate that the volume of tissue behind the globe increases. The complete bony orbit offers no point for expansion except

TABLE 1. A CLASSIFICATION OF EYE SIGNS

Group I Signs associated with thyrotoxicosis of Graves' disease (rare in malignant exophthalmos)	*Group II* Signs not necessarily associated with thyrotoxicosis (predominant in malignant exophthalmos)
Stare, and tension of musculature around eyes	True forward displacement of globe (as determined by measure)
Lid retraction Lid lag Globe lag	Gritty sensation in eyes Lacrimation Photophobia Edema of conjunctiva
Lids often less bulging; show characteristic folds, which are exaggerated by weight loss	Bulging of the lids, especially at points where retrobulbar tissue protrudes around globe
Soft cushion effect when pressure applied to globes	Resistance when pressure applied to replace globe backward
Little if any extra-ocular muscle weakness; no diplopia	Often extra-ocular muscle weakness or paralysis; frequent diplopia

Of the signs in *Group I* which lead to an impression of exophthalmos, the stare and lid retraction are most important. These two signs rapidly disappear following thyroidectomy. Their rapid disappearance masks the increase in proptosis that usually takes place.

anteriorly. The eye occupies only four tenths of the total area of this outlet (35). The pressure behind the globe tends to cause the extrusion of fat through certain hiatuses around the globe, as seen in Figure 1. These points of less resistance are bounded by more resistant structures such as the rectus muscles. The bulging of the upper lid thus characteristically occurs more strikingly under the lateral portion of the lid where there is more space. Protrusion also occurs to some extent medially above the inner canthus.

The lumpy bulging in the lateral portion of the lower lid, often beyond the malar bone, represents lobules of extruding fat.[2] As the conjunctival swelling progresses, the lids no longer completely cover the globe. Eventually, due to chronic exposure, the cornea becomes ulcerated and may perforate, resulting in the loss of the eye. Some time during the development of this condition, many of these patients begin to complain of diplopia which may

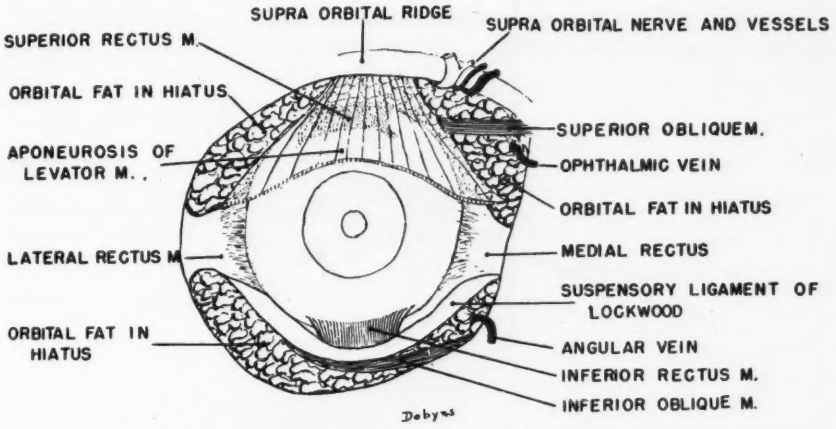


FIG. 1. The relationships of anatomic structures in the anterior portion of the orbit (modified from *McHugh*, artist). Illustrating the various areas through which fat bulges when the retrobulbar tissue volume is increased. Hiatuses between the rectus muscles define the location of protrusion so that bulging of the lids takes place in a characteristic fashion. The globe occupies about 4/10 of the orbital outlet.

progress to gross paresis or paralysis of various rectus muscles. Weakness of elevation is most common but in many extreme cases the globes become almost completely immobile. Rather severe ophthalmoplegia has been reported in some cases with relatively little proptosis. More will be said of this subsequently.

Clinicians from the time of Von Graefe (36) in 1868 have assessed evidence of pressure in the retrobulbar tissue by pressing on the globes over the closed lids. A sense of increased resistance to backward displacement and a simultaneous exaggeration of the peripheral bulging around the globe give further evidence of retrobulbar pressure. For a long time, Means (30) urged the construction of a precise instrument for the measure of resistance to backward displacement of the globes as a diagnostic and research tool.

[2] This description does not imply that this fat was previously retrobulbar, but merely refers to that fat which surrounds the globe deep behind the lids (Fig. 3).

Copper (37), acknowledging Means' suggestion as a stimulus for his investigation, devised an orbitonometer. He has clearly shown that by applying increments of force to the globe, there is noticeably less displacement in patients with malignant exophthalmos than in normal subjects. Figure 2, which is taken from his monograph,[3] graphically illustrates his findings.

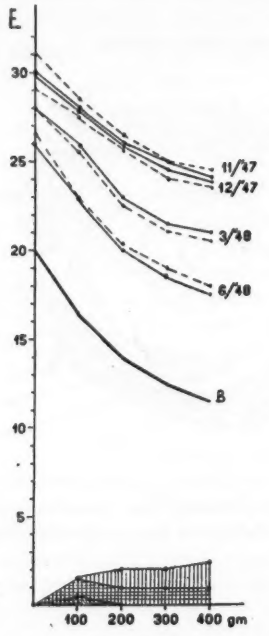


FIG. 2. Measurements obtained with an orbitonometer in a patient with malignant exophthalmos, as compared to a normal subject (from *Copper* (*37*)). Points on graph show millimeters of backward displacement (ordinate) produced by various grams of force (abscissa) applied to the globe.

Line B represents the usual backward displacement found in a normal individual. Dated lines, from above down show gradual improvement in the displacement in a patient whose disease was regressing. Broken lines = right eye; solid lines = left eye. A progressively sharper decline of the lines shows return toward normal displacement.

Further evidence of pressure in the retrobulbar tissues is probably manifest by the engorgement of retinal veins. In a review of the published cases of severe progressive exophthalmos this was described in only 15 instances. It seems probable that more of the patients demonstrated venous engorgement, but due to the inadequacy of some of the reports or the ex-

[3] Reproduced by permission of A. C. Copper.

aminations, this fact was overlooked. Papilledema was likewise infrequently mentioned. Poppen (38) in his series of 28 cases reported retinal vein engorgement in 6 and papilledema in 16. From the more adequate descriptions it seems that when these features do appear, they do so very late, when the pressure is extreme and loss of the eye is imminent.

ANATOMIC RELATIONSHIPS IN THE ORBIT

An examination of anatomic relationships of the intraorbital tissues aids in appreciation of the probable mechanisms of some of these features which

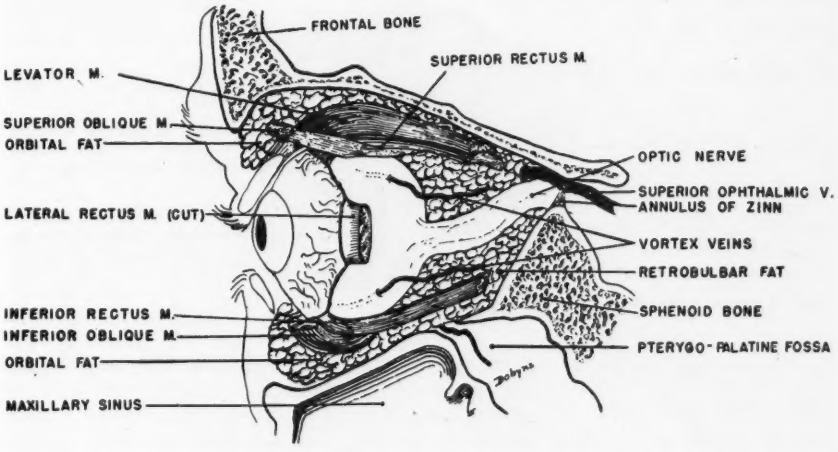


FIG. 3. Lateral view of orbital structures (modified from *McHugh*, artist). See text for description. With an increase in the volume of retrobulbar tissue and at least moderate restraint of the globe by the rectus muscles, the fat about the globe is squeezed forward beneath the lids.

have been mentioned. In Figure 3 one sees the globe with the retrobulbar structures lying behind it. The structures lie within the confines of the rigid bony orbit. The globe and the membranes extending from it to the rim of the orbit form a sensitive tambour, the septum orbitale, which reflects the changes in the volume of the tissues which lie behind it. The extra-ocular muscles arise at the apex of the orbit and insert on their respective sides of the globe near its equator, thus forming a cone. This cone of muscles is surrounded by a connective tissue sheath, the periorbita, which attaches to the anterior rim of the orbit. Fat is found within the cone of muscles and around the globe beneath the lids (*see also* Fig. 1). The veins that are seen at the periphery of the bulbar conjunctiva pass through Tenon's capsule and there, where the rectus muscles attach, communicate

with the branches of the ophthalmic veins that drain blood from the muscles. Figure 4 shows how these veins, which drain blood from the muscles, pass along the inner aspect of the muscles where they may be easily exposed to pressure within the cone. The ophthalmic veins accompanied by the ophthalmic artery and optic nerve pass through the orbital fissures at the apex of the orbit. Certain anastomotic venous branches communicate with the facial vein anteriorly, the veins of the pterygoid fossa inferiorly, the ethmoid area medially, and the supraorbital veins superiorly.

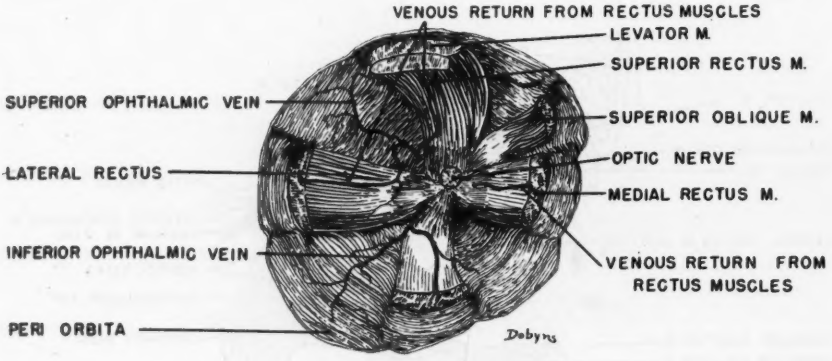


FIG. 4. A view into the muscle cone and the surrounding periorbita, with the globe and retrobulbar fat removed (modified from *McHugh*, artist). The veins which drain blood from the rectus muscles are of special interest because they lie on the inner aspect of these muscles. Pressure from within the muscle cone may compress these veins over a major portion of their course.

It should be noted, however, that the venous drainage from the muscles must enter the veins on the inner surface of the muscles before gaining final exodus through any of these routes (Figs. 1, 3, and 4).

PATHOLOGIC CHANGES IN RETROBULBAR TISSUE

Let us next consider the gross and microscopic pathology of the retrobulbar tissues. During the process of decompressing the orbit, surgeons have always found the retrobulbar tissue under pressure due apparently to an increase in volume. Naffziger (39, 40) and a host of others have placed emphasis on the space-occupying effect of enlarged extra-ocular muscles which may be many times their normal size. Under these circumstances the fat within the muscle cone may have practically disappeared. Others have noted an apparent increase in the amount of edematous orbital fat but usually have also mentioned the extra-ocular muscle changes. There is rather uniform agreement that microscopically both the fat and muscle

are edematous and infiltrated with lymphocytes and connective tissue as seen in Figures 5 and 6. This reaction microscopically simulates a chronic inflammatory process. Some of the muscle fibers appear to have lost their cross striations, suggesting degeneration. Many of the fibers are larger than normal. At times, the muscles have been found to consist of nothing but fibrous tissue (26, 40, 41). The long duration of the disease in such cases suggested that this represented the end stage of the reaction. Thus the

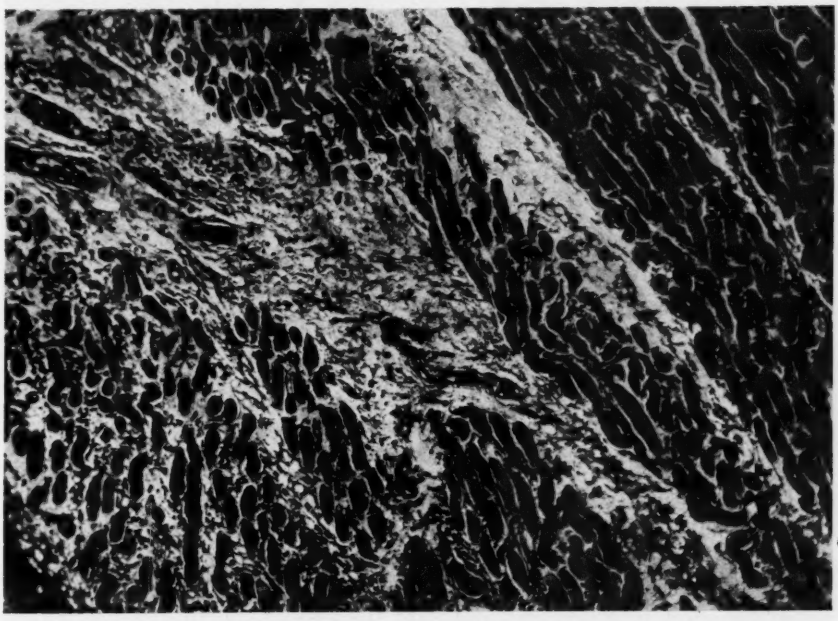


FIG. 5. Cellular edematous and fibrous infiltration of extra-ocular muscles from a patient with malignant exophthalmos (*see* Fig. 11). ×35.

differences in the pathologic findings seem to be in keeping with the various stages of the pathologic process, ranging from an acute reaction to chronic fibrosis.

CLINICAL COURSES OF PROGRESSIVE EXOPHTHALMOS

Our discussion now reaches a point when it is well to analyze the various courses that progressive exophthalmos may follow. There are admittedly all degrees of the disease from a slight increase in the prominence of the eyes to the severe proptosis which results in the loss of the eye. It seems that the disease is a self-limiting process which may or may not become arrested before the entire eye is lost. From patients observed and those

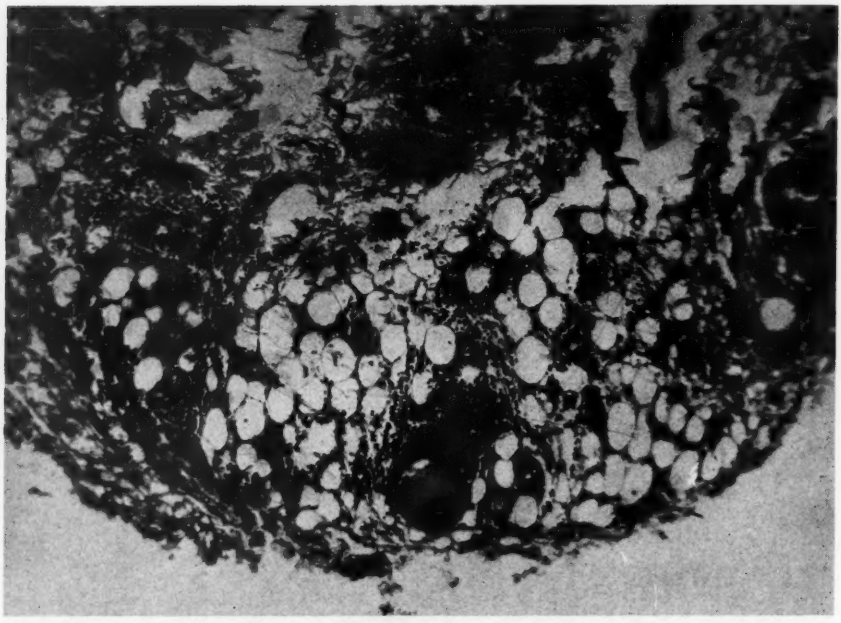


FIG. 6. Cellular, edematous and fibrous infiltration into retrobulbar fat from a patient with malignant exophthalmos (*see* Fig. 11). ×60.

described in the literature, we may graphically represent various courses that the disease may take (Fig. 7). In some patients it exhibits a very rapid development. The impression is gained that here the pressure increases swiftly within a few weeks and ulceration of the cornea may occur before time allows a compensatory lengthening of the muscles. The muscles withstand the mounting pressure and hold the globe back, thus leading to a calamity with minimal proptosis. Other cases progress more slowly. With time there may be compensation. Still others gradually develop to a state of extreme proptosis but the eyes may not be lost. The longer the disease remains active the more irreversible the condition becomes. This apparently is explained by the connective tissue that is laid down behind the globe. At any time during the development of the process the driving force behind the disease process may abate so that the exophthalmos slowly regresses and as much extra-ocular muscle function returns as reversibility will permit.

EXPERIMENTAL EXOPHTHALMOS PRODUCED BY THE THYROID-STIMULATING HORMONE (TSH)

What bearing may animal experiments have on the understanding of this disease? Smelser in 1937 (42) pointed to the similarity between the

microscopic pathology in the retrobulbar tissues of man and those of animals which had been made exophthalmic with the thyroid-stimulating hormone (TSH). Several of us (Paulson (43, 44), Aird (45), Dobyns (46)) have subsequently confirmed the finding of lymphocytic and fibrocytic infiltration accompanied by edema in the orbits of guinea pigs. In addition we (Smelser (47), Dobyns (46, 49, 50)) have shown that the reaction was present in other fat depots of the body of such animals. Paulson (48) proved the presence of edema by showing an increase in the water con-

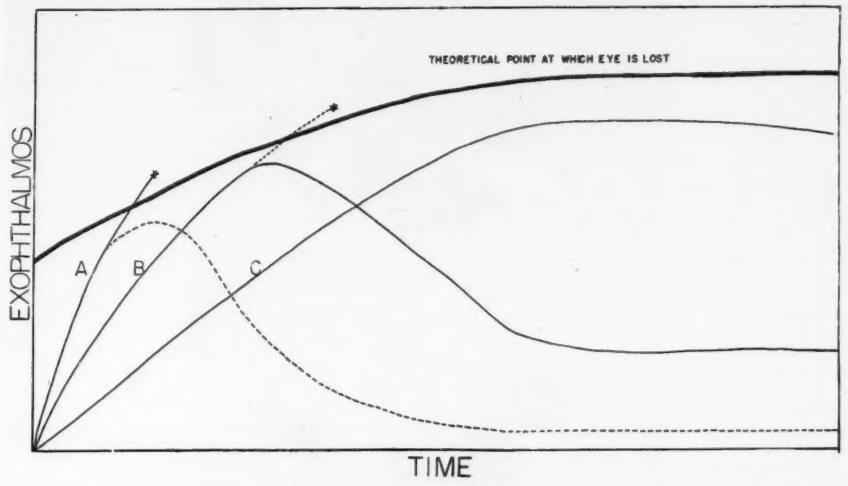


FIG. 7. Schematic representation of the courses that progressive exophthalmos may follow. Heavy black line represents a theoretic point at which the eye may be lost. Proptosis, which develops over a long period of time, may become extreme without loss of the eye. Usually the longer the active process continues the more irreversible the proptosis becomes. At any time, the progress of the disease may abate and the eye recede as much as reversibility will permit.

tent of orbital tissues. Further study (Dobyns (46, 49, 50)) on the development of the process revealed that early in the reaction there were many polymorphonuclear leucocytes and later these were replaced by tissue macrophages and lymphocytes. The tissue reaction and its associated edema resembled the reparative process following fat necrosis. Collagenous connective tissue was laid down as time went on, a finding compatible with Friedgood's observation (51) that long standing exophthalmos was less reversible than that of shorter duration. It was also noted that these animals presented evidence of very rapid mobilization of fat because the plasma fat levels rose, the polymorphonuclear leucocytes of the circulating blood contained phagocytized fat, and fat soon appeared in abnormal

amounts in many tissues, particularly the liver and striated muscle. This occurred at the same time that the fat depots were depleted of fat and replaced by edema, cellular elements and connective tissue. Fat-stained preparations of fat depots showed many fat droplets in the cytoplasm of

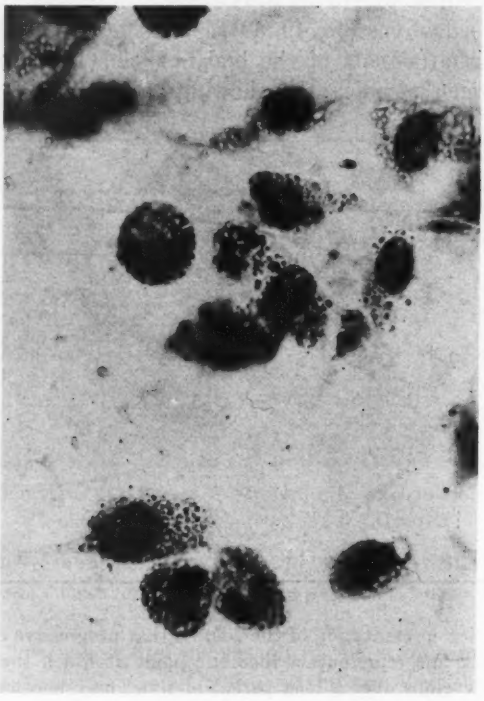


FIG. 8. Phagocytosis of fat by polymorphonuclear leucocytes and macrophages in a fat depot from a guinea pig which had been given TSH (from *Dobyns* (*49*). Courtesy *Surg., Gynec. & Obst.*). This reaction is accompanied by edema and a rapid depletion of fat from the depot. ×750, as illustrated here.

the phagocytic cells that had arrived on the scene (Fig. 8). Stainable fat appeared in muscle fibers in many locations, especially in the extra-ocular muscles (Fig. 9). These observations were interesting, since the tissue reaction developed concomitantly with the exophthalmos and was not dependent on the presence of the thyroid (Fig. 10).

COMPARISON OF THE PATHOLOGY IN EXPERIMENTAL ANIMALS AND MAN

In 1942 at the Mayo Clinic, the author studied specimens of the orbital contents from 4 patients who had had enucleation of one or both eyes because of malignant exophthalmos. Microscopic sections of these tissues

were stained by the following techniques in order to compare the changes with those in the animals: hematoxylin and eosin, Mallory-Heidenhain, van Gieson, and fat stains (frozen sections) (Table 2). The characteristic infiltration of orbital fat and muscles with edema, lymphocytes and macrophages was observed as has been reported by other authors (39, 42). In

TABLE 2. A SPECIAL STUDY OF THE HISTOLOGIC CHANGES IN THE ORBITAL TISSUES FROM PATIENTS WHO HAD UNDERGONE ENUCLEATION OF ONE OR BOTH EYES OR ORBITAL DECOMPRESSION

Case	Sex	Age (yrs.)	Presence of cellular infiltration*	Phagocytosis of fat in macrophages and polymorphonuclears	Presence of young connective tissue shown by differential staining)	Homogenous eosinophilic material infiltrating fat	Edema	Remarks
1	M	?	Marked	Extreme	Considerable	Mild to Marked	Marked	Mayo Clinic 1938; exophthalmos; mild if any thyrotoxicosis; thyroidectomy; enucleation one eye; orbit filled to level of remaining eye
2	F	7	Marked	Marked	Extremely abundant	Extreme	Marked	Mayo Clinic 1920; exophthalmos predominantly unilateral; enucleation
3	F	56	Mild	Questionably present	Comparatively little	Mild	Mild	Mayo Clinic 1923; mild thryotoxicosis; enucleation of one eye; other eye became useless
4	F	50	Marked	Marked	Extremely abundant	Marked	Extreme	Mayo Clinic 1916; mild thryotoxicosis; pole ligation; ganglionectomy; bilateral enucleation
5	M	38	Moderate	Marked	———	Mild	Moderate	Mass. Gen. Hosp. 1949; thyrotoxicosis; thyroidectomy followed by hypothyroidism and exophthalmos: bilateral Naffziger operation

* Reactions in tissues graded as Mild, Moderate, Marked or Extreme.

It should be noted that the material on the first 4 cases had been preserved in fixative for a long time before this histologic study was made.

addition, both young and old forms of connective tissue were present. The phagocytosis of fat in large tissue macrophages similar to that in animals (46, 49, 50) was found; this had not been previously reported. Because these patients were not personally observed, the possibility of extensive infection (which would lead to phagocytic activity) could not be ruled out. Therefore, the results were not published.

Recently at the Massachusetts General Hospital, we have had the opportunity to observe a man[4] of 38 years of age with rapidly developing and

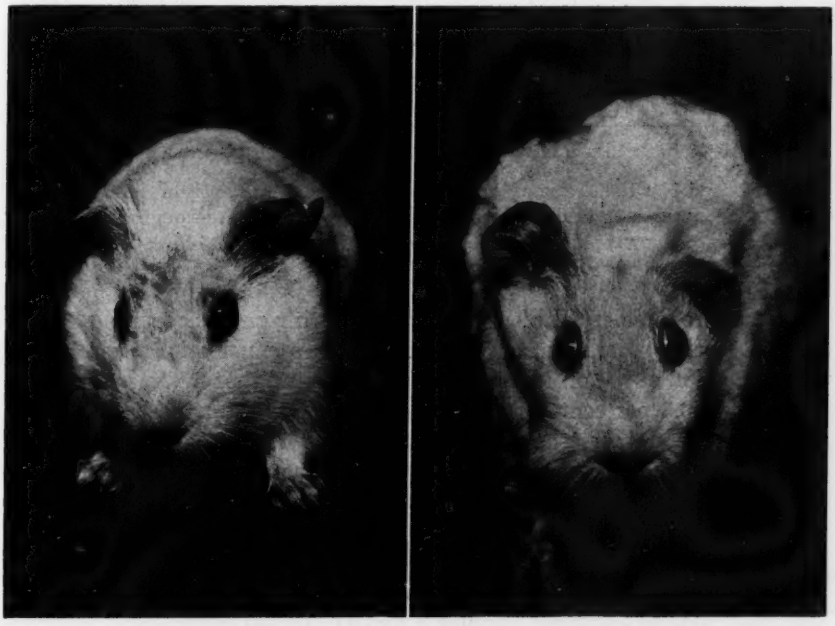
[4] *See* Table 2, Case 5.

severe malignant exophthalmos. A thyroidectomy had been performed elsewhere for thyrotoxicosis, after which marked hypothyroidism had ensued. Figure 11 illustrates the extreme chemosis and proptosis in this man. Dr. J. C. White decompressed the orbits through a bilateral transfrontal craniotomy. When the periorbita was incised, fat bulged forth. In

FIG. 9. Fat droplets in skeletal muscle fibers of a guinea pig given TSH (from *Dobyns* (*46*). Courtesy, *Surg., Gynec. & Obst.*). The appearance of fat in the extra-ocular muscles is usually more striking than that seen in other skeletal muscles. ×124, as illustrated here.

this case, there was nothing to suggest infection except the slight purulent discharge at the lid margins. In fat-stained preparations under high magnification phagocytized fat was clearly seen in large tissue macrophages and polymorphonuclear leucocytes. This was similar to the picture which was seen in animals which had been given TSH (compare Fig. 8 and Fig. 12). These cells, along with many lymphocytes, were invading retrobulbar fat and muscle. The hematoxylin and eosin sections of extra-ocular muscles revealed spotty areas of granularity and loss of the striations. The fat

stains, just as had been seen in the guinea pig, showed these areas of the muscle to be ladened with minute droplets of fat (compare Fig. 9 and Fig. 13). It will be noted in Figure 13 that the large tissue macrophages which surround the fiber contain phagocytized fat. The repetition of the finding



A B

FIG. 10 Exophthalmos in a guinea pig which had been given TSH (from *Dobyns* (*56*). Courtesy, *Surg., Gynec. & Obst.*). A. Normal control animal. B. Animal treated with TSH. Since the orbit in the guinea pig is less complete than that of man, the expansion to retrobulbar tissue is not entirely in the anterior direction in this animal.

of phagocytosis of fat in fresh tissue in this new case and the new observation of fat deposited in muscle fibers confirms the reliability of the observations. Although TSH assays have not been available in this case, the observations make one feel that there is more than a casual similarity in the reaction in animals given TSH and patients suffering from malignant exophthalmos.

THE SIGNIFICANCE OF PHYSIOLOGIC FACTORS SUCH AS SEX AND AGE

What physiologic factors have a bearing on malignant exophthalmos? After reviewing all reported cases (359 patients) in which the age and sex are recorded, it was found that 55.9 per cent of these were males and 44.1

TABLE 3. THE AGE AND SEX DISTRIBUTION IN PATIENTS WITH SEVERE PROGRESSIVE EXOPHTHALMOS*
Number of cases by decades

	0–10	11–20	21–30	31–40	41–50	51–50	61–70	71–80	*Total*	Per cent of cases	Average age
Males			7	23	20	20	11		81	55.9	46.5 yrs.
Females	2	3	11	12	20	13	2	1	64	44.1	40.5 yrs.

Total number of cases including those for which age or sex not stated—359

* The criteria for the choice of these cases were chemosis, paresis or paralysis of the extra-ocular muscles, corneal ulceration, enucleation, or orbital decompression accompanying progressive exophthalmos. Age was specifically given in 145 out of 359 cases.

per cent were females (Table 3). After considering only those patients who showed corneal ulceration, or were subjected to enucleation of an eye or decompression of the orbit (65 cases), it was found that 67.7 per cent were males and 32.3 per cent were females (Table 4). Since the number of females far outnumbers that of males in classic Graves' disease, this predominance of males among patients with malignant exophthalmos is probably significant. The fact remains that some of the cases in females represent an extreme degree of the disease.

When the ages of these patients were considered, it was found that they involved many decades of life. The average age of the female was slightly less than that of the male (Tables 3 and 4). Although one commonly associates this disease with adult life, the fact that severe cases (32, 52, 53)

TABLE 4. SEX AND AGE DISTRIBUTION IN CASES FROM THE LITERATURE IN WHICH CORNEAL ULCERATION DEVELOPED, OR IN WHICH THE PATIENT WAS SUBJECTED TO ENUCLEATION OF AN EYE OR DECOMPRESSION OF THE ORBIT*
Number of cases by decades

	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	*Total*	Per cent of cases	Average age
Males			3	13	13	8	7		44	67.7	46.4 yrs.
Females	1	1	3	7	4	4	1		21	32.3	38.4 yrs.

Total number of cases including those for which age and sex was not stated—226

* This group of cases does not include the series by Sattler (32), VonGraefe (31), Naffziger (80), or Poppen (38), because specific ages were not given.

(Table 2) have been reported in children (ages 2½, 6, 7 and 10 years) raises the question of whether sex hormones play an important part.

Marine and Rosen (54, 55) reported that gonadectomy abolished the exophthalmos produced in guinea pigs with methylcyanide. In the author's own experiments (50, 56), exophthalmos was produced with TSH just as readily in gonadectomized animals as it was in normal animals.

FIG. 11. Malignant exophthalmos in man following subtotal thyroidectomy. The rapidity and severity of exophthalmos made orbital decompression urgent. Lids of left eye have been sutured to protect the cornea.

THYROID-STIMULATING HORMONE (TSH) AND EXOPHTHALMOS

The problem of whether TSH is responsible for exophthalmos in man remains an intriguing question. The rise of TSH in the blood and urine after thyroidectomy and various thyroid-pituitary relationships have led to the theory of a balance between thyroid hormone and TSH. More recent methods of assay support the earlier reports that TSH is very low in classic Graves' disease but is elevated after thyroidectomy and is elevated in many cases of malignant exophthalmos (57–65). We have observed that there is an increase in the prominence of the eyes after thyroidectomy (33) (Fig. 14). Dobyns and Haines have observed (66) a further increase as myxedema develops; then in the same patients they have reversed it, in

a measure at least, by administering desiccated thyroid (Fig. 15). Patients with spontaneous myxedema when treated with desiccated thyroid similarly experience a decrease in the prominence of the eyes (Fig. 16). However, in one of our patients who was thought to have the anterior pituitary failure of Sheehan's disease, the eyes receded as in the other patients with

FIG. 12. Phagocytosis of fat by polymorphonuclear leucocytes and macrophages in the retrobulbar fat from a patient with malignant exophthalmos (*see* Fig. 11). Scharlach R and hematoxylin (fat stain). Compare with reaction seen in the guinea pig given TSH (Fig. 8). ×750.

classic myxedema. The eyes increase in prominence when Graves' disease is treated with thiouracil (Fig. 17). Indeed, in one of our patients, severe progressive exophthalmos began shortly after such therapy was instituted. Whether mild changes in the prominence of the eyes represent the same mechanism that produces malignant exophthalmos, we cannot say.

The assays by Purves and Griesbach (64) and Del Conte (65) would indicate that thiouracil treatment of Graves' disease results in a rise in TSH. The observation of Rawson, Graham and Riddell (67) that thyroid tissue, especially hyperplastic tissue, inactivates TSH may be related to

FIG. 13. Fat droplets in a fiber of extra-ocular muscle from a patient with malignant exophthalmos (*see* Fig. 11). Scharlach R and hematoxylin (fat stain). Note numerous macrophages which contain fat and surround this involved muscle fiber. Compare with the reaction seen in skeletal muscle of a guinea pig given TSH (Fig. 9). ×140.

the rise in this substance after thyroïdectomy. At any rate, the advancement of our knowledge of the relation of TSH to exophthalmos awaits the availability of a simple and reliable method of assay.

RESULTS OF THERAPEUTIC MEASURES AS A KEY TO THE MECHANISM OF EXOPHTHALMOS

How do the results of various methods of treatment contribute to our knowledge of the mechanism of exophthalmos? First, there seems to be no method which gives uniformly successful results except adequate surgical decompression. Second, there is frequently spontaneous recovery which confuses our evaluation of treatment. Third, various methods of therapy are applied to patients whose disease has reached an irreversible state, at which time correction of the cause does not necessarily remove the firm connective tissue that has been laid down behind the globe.

Dehydration usually causes temporary improvement, but the slack

thus produced is soon taken up by the progress of the disease. Similarly patients learn to sleep in an upright position in order to avoid the increase in edema which is caused by lying down.

Thyroid administration has been used after the suppression of thyrotoxicosis with iodine. In theory this may suppress the pituitary function;

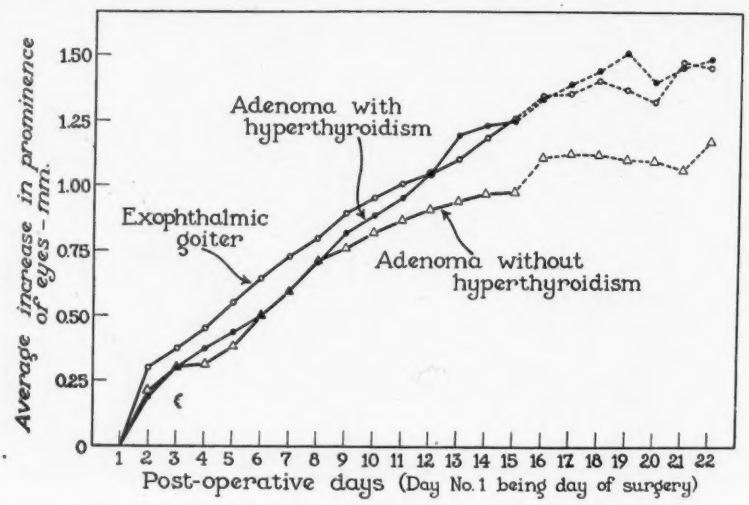

Average increase in prominence of eyes - mm.
1.50
1.25
1.00
0.75
0.50
0.25
0
Adenoma with hyperthyroidism
Exophthalmic goiter
Adenoma without hyperthyroidism
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Post-operative days (Day No. 1 being day of surgery)

FIG. 14. Increase in the prominence of the eyes following thyroidectomy (from *Dobyns* (*33*). Courtesy, *Surg., Gynec. & Obst.*). This represents a composite of individual graphs made for each of 233 patients and based on more than 10,000 eye measurements. After the fifteenth day the number of patients represented begins to diminish considerably. This is made evident by the broken lines. The incomplete data of the third week are presented in order to illustrate the diminishing rate of change.

or perhaps benefit is derived from the diuretic effect of thyroid, especially if the metabolism is low. In many mild cases this procedure seems to be helpful; however, the fact remains that many of us have seen cases progress to an extreme degree in spite of this therapy. Some of these patients tolerate enormous doses of desiccated thyroid without exhibiting undue toxicity. Purves, during his recent visit to this country, told us of a patient to whom he had given 100 grains of thyroid daily for fourteen days. The fact that we often see an increased tolerance to thyroid among these patients might mean that there is an unusually low end-organ sensitivity to thyroid hormone, thus inducing excessive TSH output.

In the literature, we found 2 cases of severe exophthalmos treated with estrogenic substances. It is not clear that any benefit was derived from this therapy. Although it may be argued that estrogens suppress the ante-

rior pituitary, it should be recalled that they cause water retention in tissue.

Thirty-seven cases described in the literature were treated with roentgen irradiation to the pituitary. Of these, 13 were benefited. In many instances, the dosage of irradiation was not recorded. Because of possible serious side

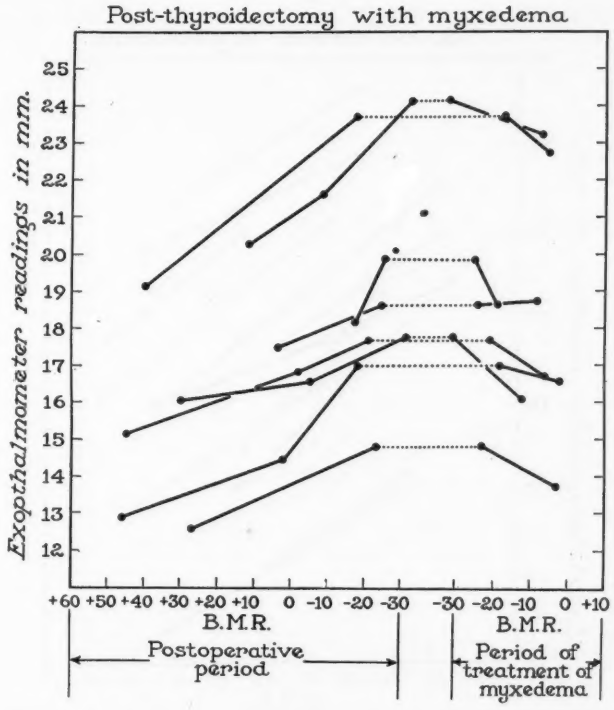


FIG. 15. Changes in the prominence of the eyes in patients in whom myxedema developed after thyroidectomy (from *Dobyns and Haines* (*66*). Courtesy, *J. Clin. Endocrinol.*). The increase in the prominence of the eyes is at least partly corrected by the administration of thyroid.

effects, its use seems to have been confined to the more severe cases. A sufficient number of patients seem to have improved so that the method should be further considered.

Much attention should be given to results of electrocauterization of the pituitary by McCullagh, Ruedeman and Gardner (68). At the time of the decompression of one orbit the pituitary was destroyed. In all 4 of their patients the eye whose orbit was not decompressed regressed appreciably. The fact that in all 4 of these cases the eyes regressed seems highly signifi-

cant, even though Naffziger (69) has seen regression in one orbit after decompression of the other.

A POSSIBLE MECHANISM OF PROGRESSIVE EXOPHTHALMOS

What theory of the mechanism of exophthalmos fits the largest number of acceptable findings? The increase in the volume of retrobulbar tissue

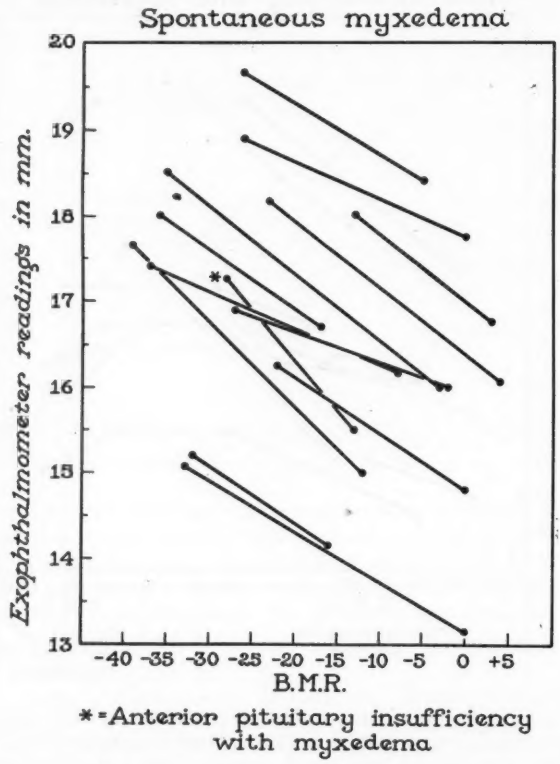


FIG. 16. Changes in the prominence of the eyes of patients with spontaneous myxedema treated with desiccated thyroid (from *Dobyns and Haines (66)*. Courtesy, *J. Clin. Endocrinol.*). The eyes decrease in prominence as the basal metabolic rate rises.

seems adequately demonstrated by the pressure observed at the time of decompression of the orbit and by the picture described by orbitonometric measurements. TSH or some substance from the anterior pituitary may cause the connective tissue reaction as it does in animals. The accompanying edema may explain much of the increased volume.[5] It seems quite pos-

[5] Rundle and Pochin (70) reported no increase in the water content of retrobulbar

sible that the reaction in man is similar to that produced in animals by anterior pituitary preparations, presumably TSH. That the very severe phase of the process cannot be produced in the animal is explained by the

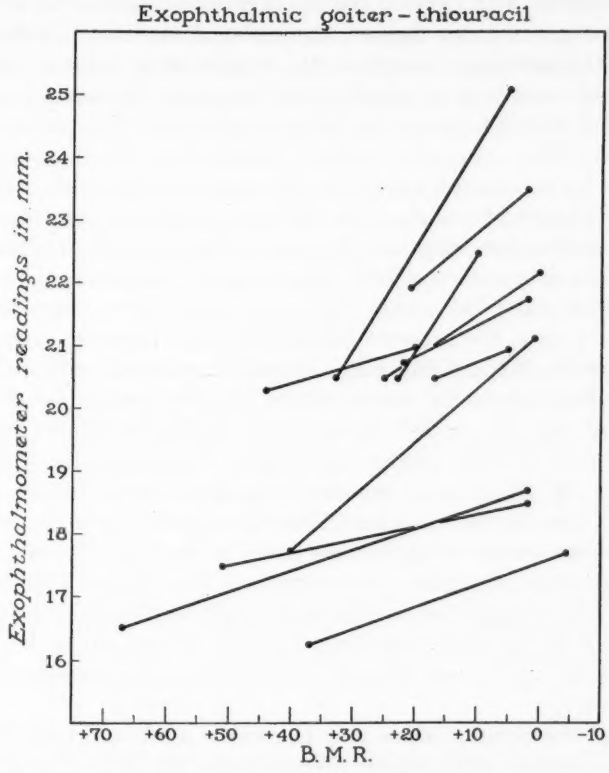


FIG. 17. Changes in the prominence of the eyes in patients who were treated with thiouracil for Graves' disease (from *Dobyns and Haines* (*66*). Courtesy, *J. Clin. Endocrinol.*).

tissues of patients dying of Graves' disease: but in a recent discussion before the Royal Society of Ophthalmology, Pochin (71) discussed this former paper and pointed out that none of these patients with Graves' disease had severe exophthalmos. They did find a slightly less than twofold increase in the fat content of extra-ocular muscles. Since fat normally makes up only 8.1 per cent of the muscle and the muscle represents only part of the total of retrobulbar tissue, one might question the contribution that this increase in fat makes to the total volume. Their published data also showed that the increase in the fat content of the muscles was essentially the same, whether the patients had exophthalmos or not. The increase in lipoid in the adipose tissue was only slightly increased above normal. The authors raised the question of the significance of this increase.

incomplete orbit, a state comparable to that created by the surgeon in man in order to stop progressive exophthalmos.

The ophthalmoplegia which accompanies the reaction should be explained. It occurs with varying degrees of proptosis but, as far as we know, only after the resistance behind the globe is increased. Naffziger (72) compared the histologic changes in the muscles with those of Volkmann's palsy. In this condition, in which edema in a limb may expand against the resistance of circumferential fascia or a tight cast, the venous return is embarrassed. This results in swelling, impaired or lost function, and the infiltration by inflammatory cells in the muscle distal to the obstruction. Brooks (73) has produced the same picture in muscle by ligating the veins. A similar mechanism may be going on in the retrobulbar tissue. Let us suppose, for a moment, that TSH might cause a reaction in the connective tissue and fat which lies within the muscle cone. After progression of this process for a time, the pressure behind the globe becomes extreme. Then other factors may come into play. Expansion of tissue within the muscle cone may then impede the venous return from the rectus muscles (Fig. 4). The critical point at which venous stasis results in edema probably is reached in some muscles sooner than others. To support this theory there are reports (30, 61) of some muscles being found more swollen and some losing their function before others. That there probably is a vascular component in the course of the severe cases is seen by the rather sudden spurts that often punctuate the progress of this disease (76–79). Such a mechanism of impeded venous drainage might well explain the infrequent involvement of the inferior oblique; the body of this muscle lies in an anterior position and is not exposed so directly to the pressure within the muscle cone.

Although the initial reaction may be mostly in fat and connective tissue, the extreme muscle involvement predominates the picture by the time the surgeon is forced to decompress the orbit. If these assumptions should prove to be right, the reaction we see in animals given TSH may be the generating force which has to do with this problem in man.

SUMMARY

An analysis is made of the factors which have a bearing on the mechanism of progressive exophthalmos. The following considerations are discussed:

Theories of exophthalmos.
Circumstances under which exophthalmos is found.
Physical eye signs associated with exophthalmos.
Evidence of an increase in retrobulbar tissue volume.
Anatomic relationships in the orbit.

Pathologic changes in retrobulbar tissue.

Clinical courses of the progressive exophthalmos.

Experimental exophthalmos produced by the thyroid-stimulating hormone.

Comparison of the pathology in experimental animals and man.

The significance of physiologic factors such as sex and age.

Thyroid-stimulating hormone (TSH) and exophthalmos.

Results of therapeutic measures as a key to the mechanism of exophthalmos.

A possible mechanism of progressive exophthalmos.

An effort is made to gather together those pertinent clinical, anatomic, pathologic and endocrinologic facts which should direct us toward a future understanding of the true mechanism of progressive exophthalmos.

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THE SURGICAL TREATMENT OF PROGRESSIVE EXOPHTHALMOS*

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EXOPHTHALMOS is noted in about 60 per cent of patients with primary hyperthyroidism. In a large series of cases of primary hyperthyroidism, Cattell (1) found that 21 per cent showed persistence of the preoperative exophthalmos, but in only 1.1 per cent did an increase occur following operation. It is with the latter group that we are particularly concerned as neurosurgeons, since, in a few of these patients (approximately 1 in 1000 patients with primary hyperthyroidism) exophthalmos will progress to such a degree that orbital decompression is necessary to save the patient's eyesight. It is important to note that progressive exophthalmos does not necessarily occur in patients with primary hyperthyroidism. In 2 patients chronic thyroiditis was the etiologic basis, and in 6 patients toxic adenoma; the other 58 patients had primary hyperthyroidism.

Naffziger (2), in 1931, first described a surgical technic for the relief of certain patients in whom the severe form of progressive exophthalmos develops. By means of this technic he was able to decompress the orbital contents transcranially. Because of this foresight the eyeballs of many patients have been saved in recent years. Previous surgical attempts had failed to save the eyeballs in severe progressive exophthalmos in most instances. In only the less malignant cases did canthotomy, canthoplasty and tarsorrhaphy, sympathectomy and other less radical attempts at orbital decompression save the eyeballs.

Our experiences with orbital decompression began in 1933 (3) (4). Sixty-six patients have been operated on for severe, progressive exophthalmos. Of these, 26 were males and 40 females. Their ages ranged from 27 to 67 years.

The indication for orbital decompression is progressive exophthalmos in the presence of increasing visual change. Subjectively, protrusion of the eyeballs, diminished, blurred or double vision and also a sensitiveness to light and excessive lacrimation may be noted. Objectively, there is swelling

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of the eyelids, chemosis and at times keratinization of the conjunctiva. External ocular muscle palsies are noted in most instances. The power of convergence is frequently impaired. Limitation of movement of one or both eyeballs in one or all phases may be seen. In our group of cases the upward gaze was considerably limited. In one instance there was complete ophthalmoplegia bilaterally. In 6 patients considerable care had to be exerted to keep the eyelids partially closed so that they would not retract behind the eyeball. Corneal ulceration, recent or old, was present in several patients. The wedge shaped areas of discoloration of the conjunctiva in the medial and lateral portions of the eyeballs are indications of exposure and usually mean the patient's eyelids do not close completely at any time.

These progressive symptoms should seriously concern all of those who come in contact with these patients. Exophthalmos that is progressive should be observed closely by the internist, ophthalmologist and the neurosurgeon so as to determine the course of treatment and, if surgery is indicated, to decide the optimum time. This, naturally is variable and will depend to some extent on the individual's previous experiences and observations. It is reasonable to state that in the presence of severe, progressive exophthalmos associated with changes in vision in a patient without thyroid toxic symptoms with a normal or subnormal basal metabolic rate, orbital decompression is indicated. The increase in retro-orbital resistance to pressure on the eyeball with the palpating finger is an important finding. In none of the patients subjected to orbital decompression was the retro-orbital resistance normal. Patients with marked exophthalmos with little or no increase in retro-orbital resistance usually are in no danger of losing their eyeballs unless the exophthalmos is so great that corneal ulcerations occur or that atrophy is taking place in the optic nerve.

The measurement of exophthalmos by the grading system is valueless unless the grading is done by one individual. False impressions are easily obtained due to the puffiness of the eyelids or variable degrees of conjunctival edema. The exophthalmometer in experienced hands is of utmost value for noting accurately the degree of exophthalmos. It is true that in a few instances the degree of exophthalmos may be less marked in a patient with a fulminating so-called malignant exophthalmos than in a patient whose eyeballs are not in jeopardy.

In the 66 patients, the preoperative maximum degree of exophthalmos was 37 mm. and the minimum 19 mm. In 10 of the 66 patients the protrusion was 25 mm. or more. In only 8 patients were the measurements exactly the same for each eye. The others varied up to 6 mm. The progressive stage of exophthalmos appeared in two weeks to twenty-five years following thyroidectomy, although some degree of exophthalmos was usually present at the time of thyroidectomy. The average length of time

between the thyroid operation and the orbital decompression was four years. In 2 patients x-ray treatment for hyperthyroidism had been successfully carried out elsewhere ten years and two months respectively, before orbital decompression had become necessary. Marked progressive exophthalmos causing visual changes necessitated orbital decompression in 2 patients one month and four months respectively, before thyroidectomy became necessary for the hyperthyroidism. These patients had low metabolic rates and no evidence of hyperthyroidism other than progressive exophthalmos at the time of the orbital decompression.

There appeared to be no relationship between the rapidity of the development of exophthalmos and extra-ocular muscle palsy. The muscle palsies occurred more frequently in patients with a moderate degree of exophthalmos than in those with severe protrusion of the eyeballs. It is in these patients that a brawny-like edema takes place in the retro-orbital tissues, and in most instances at the time of orbital decompression there is very little fatty tissue, the intra-orbital space being occupied by pale, firm, greatly enlarged orbital muscles.

The basal metabolic rates in most instances were below normal, being as low as minus 20 per cent in 6 patients. In only 4 patients was the basal metabolic rate above normal.

The differential diagnosis of progressive exophthalmos is usually not difficult except in instances in which one eye is primarily affected. In these individuals, orbital tumors, an infectious process, cavernous sinus thrombosis, congenital malformations and arteriovenous aneurysms must be considered. However, the high incidence of extra-ocular muscle palsies in patients with exophthalmos due to thyroid disease is of definite help in making the diagnosis.

Before orbital decompression is actually decided on, conservative measures should be instituted, such as limitation of fluid intake, reduction in weight whenever the patient is obese, and administration of desiccated thyroid when generalized myxedema is obvious. Procrastination of operation should not be tolerated when visual loss is detected and if all palliative therapy has been of no benefit. Orbital decompression for cosmetic effect should not be encouraged unless that patient's livelihood depends on his or her appearance.

The surgical technic used remains essentially the same as described by Naffziger (2, 5, 6, 7) in his original and subsequent papers, with certain modifications together with a few preoperative and postoperative suggestions which we have found helpful.

It has been our custom to suture the eyelids temporarily with interrupted mattress sutures of black silk, just before the decompression. This is done immediately following the induction of anesthesia. It not only improves the operative result but reduces to

a minimum the postoperative conjunctival edema and safeguards formation of corneal ulcers.

A modified coronal incision is made with the scalp flap being reflected to the supra-orbital ridges. A small triangular bone flap is made in each frontal region, the bony openings being made with a small trephine electric drill; this permits replacement of the bone buttons at the completion of the operation and prevents bony deformity as a result of the operation. The dura is separated from the orbital plate, and the temporal muscle is separated from the lateral margins of the orbit. The roof of the orbit, the sphenoid wing, the lateral margin of the orbit to the inferior orbital fissure as well as the roof of the optic canal are removed. Whenever large frontal ethmoid or frontal sinuses are present, they are opened and the mucous membrane is gently peeled from the walls of the sinus; if not large, the mucous membrane is left intact. If an opening is made in the membrane the folds will fall together. These membranes are then sealed with gelfoam impregnated with one of the sulfa powders. The inferior wall of the frontal sinus is removed only in the large extensions, where adequate decompression cannot be obtained in any other manner. Many times more adequate decompression can be obtained by removing the inferior portion of the orbital rim superiorly. The peri-orbital fascia is then incised and may be utilized as an added protection to cover an opened sinus with a pedicle flap of the fascia. The extra-ocular muscles and fatty tissue will bulge through the opening made in the peri-orbital fascia. We have not felt it necessary to obtain muscle biopsy specimens in any of our recent cases, as the microscopic sections demonstrate fragmentation and edema of the individual muscles in all patients. It has also been my impression that extra-ocular muscle palsies may possibly be increased by taking a biopsy specimen. Certainly, we have been cautious not to incise the annulus of Zinn, since this definitely will increase or produce extra-ocular muscle palsy. A small catheter is used on each side, both for drainage and for instilling penicillin postoperatively if the sinuses have been opened. The scalp flap is replaced and closed with through-and-through interrupted black silk sutures.

Upon removal of the drapes at the completion of the operation, the eyes show immediate marked recession, and some pulsation is noted. The eyelids which have been previously sutured are covered with boric strips and a rubber bag (condom) partially filled with air is placed over each eye and kept in place with Ace bandages. This allows firm pressure over the eyes which is relatively comfortable for the patient and also will prevent ischemia from too tight pressure.

When orbital decompression was first suggested it was performed unilaterally even if both eyes were involved. Bilateral decompression can be done simultaneously by two surgeons in a relatively short time, taking an hour and a half to two hours to complete the operation. We believe that the bilateral procedure is indicated in all cases associated with hyperthyroidism, since in most patients both eyes are involved eventually. Complete radical decompression is necessary to produce the desired results.

The immediate postoperative reduction in the exophthalmos is always dramatic. It is important that firm pressure be kept over both eyes, since any swelling that takes place will occur in the tissues behind the orbital rim, rather than anteriorly. For that reason it is necessary that the pressure remains constant for the first seven days following the operation; the

pressure is released daily during the period while the wound is being dressed. Many weeks and months of chemosis are avoided in that way and the improvement has remained more satisfactory than before the use of constant pressure on the orbits.

There has been no operative mortality. The postoperative complications have been transient. With the more radical decompression, both the cosmetic and visual results have improved. Long standing extra-ocular muscle palsies have been slow to recover and have been permanent in 8 patients. Diplopia has not been a factor after one year following operation even in patients with extra-ocular muscle palsies, since the patients learn to ignore one image. In the first patient subjected to orbital decompression in 1933 with exophthalmos marked in one eye, a small decompression was carried out unilaterally because of large paranasal sinuses. Several months later the other eye became markedly involved. The patient refused further surgery. Corneal ulceration resulted in panophthalmitis, meningitis and death. In 3 patients frontal lobe signs developed following operation; these occurred in the earlier cases in which large frontal flaps were turned down, permitting more pressure on the frontal lobes. It is fair to say, however, that in one of these patients following thyroidectomy a psychosis developed of such a degree that it was necessary to send him to a psychopathic hospital for management; he recovered spontaneously. Following the use of a smaller bone flap we have not noted frontal lobe signs as a result of swelling of the frontal lobes in any of the patients.

In all patients subjected to orbital decompression the eyeballs were saved and the vision improved. In 2 patients, before the days of chemotherapy, incomplete decompressions were carried out, making it necessary for the otolaryngologist to exenterate the maxillary, ethmoid and frontal sinuses to allow a satisfactory decompression.

The amount of recession is usually in direct proportion to the degree of exophthalmos and, therefore, one cannot give the average reduction of exophthalmos in a group of patients except perhaps to give the maximum reduction, which was 10 mm., and the minimum, 4 mm. Gradual recession in the exophthalmos has continued in patients over a period of years.

There is an optimum time for orbital decompression. Operation should not be withheld until severe chemosis and perhaps corneal ulceration have developed. Indications for the procedure are progressive exophthalmos of a high degree and progressive visual changes.

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CLINICAL EXPERIENCE WITH THE BLOOD PROTEIN-BOUND IODINE DETERMINATION AS A ROUTINE PROCEDURE*†

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THIS paper presents some of the ten-year experience of the Los Angeles County Hospital with blood iodine determinations, which are done as a routine procedure in the general chemistry laboratory of the hospital and in the private laboratory of one of the authors (A.L.C.). *It is not the purpose of this discussion to attempt to establish a set of precise values for protein-bound iodine in various accurately defined disease states,* but rather to report the values that have been obtained in "routine" hospital practice in these states. The material has been drawn from special studies on patients seen in the thyroid clinic and from the clinical records of the Los Angeles County Hospital, from the present back to 1938. Experience in therapeutic studies with this procedure for determining blood protein-bound iodine (PBI) during a two-year study in which hundreds of tests were made in the serial observation of hyperthyroidism treated with antithyroid drugs indicated its reliability and usefulness in measuring thyroid activity as it rose and fell under treatment (1–3). In general, it is the opinion of our staff that the procedure may be maintained on an economical basis and that the results are precise enough to be of clinical significance and of great practical value.

The report is divided into two general sections: 1. Laboratory problems and various artifacts. 2. Initial iodine assays in various states of health and disease.

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METHOD

The method used here has been previously described (Chaney, 1940 (4)).

The protein is precipitated from 3 cc. of plasma with tungstic acid; the precipitate is digested by a mixture of sulfuric and chromic acids. The solution is reduced by phosphorous acid and then distilled; the iodine, thus evolved, is caught in a trap containing a mixture of sodium hydroxide and sodium arsenite solutions. The iodine content is found by measuring its catalytic action on the ceric sulfate-arsenious acid reaction. This is done on a photoelectric colorimeter at a series of specified times, and the curve compared with that of a standard. In the private laboratory of one of the authors (A.L.C.), a recording colorimeter has been used. The techniques and modifications which this instrument require are described in an article now in press (5).

An analysis requires approximately three hours. A trained technician can perform from 8 to 12 such analyses, in duplicate, per day. The Los Angeles County Hospital technician performs about 200 assays per month in duplicate.

LABORATORY ERRORS AND VARIOUS ARTIFACTS

Reliability

Table 1 shows the differences found between simultaneous duplicates by the technician of the Thyroid Clinic of the Los Angeles County Hospital.

TABLE 1. RELIABILITY OF PBI DETERMINATION

Difference between duplicates run simultaneously	Average value of PBI level	
	Low, 0–7 μg.	High, 7.1–20 μg.
	No. of cases	No. of cases
0.0–1.0 μg.	69	49
1.1–1.5 μg.	6	11
1.6–2.0 μg.	3	4
2.1–3.0 μg.	1*	2*
3.1–4.0 μg.	1**	1**
Total	80	67

* Analyses repeated.
** Analyses reported as unsatisfactory.

Note that of the low-level group 86 per cent agree within 1.0 microgram; 93 per cent within 1.5 micrograms; and 97.5 per cent within 2.0 micrograms. If the discrepancy of the simultaneous duplicates is more than 2.0 micrograms, a third aliquot is run; if the discrepancy is still large, the specimen is reported as unsatisfactory. This happened once in each level.

For the whole group of 147 determinations, agreement within 2.0 micrograms occurred in 96.6 per cent. Analysis of 155 determinations by the technician doing the routine hospital chemistry showed an identical distribution of differences.

In the clinical studies to be reported later in this paper, only the first reported PBI is used for the tabulations. In Table 2 is shown the difference between the first and second reports of the PBI of 120 unselected patients, divided into two levels. Several days or more may have elapsed between

TABLE 2. COMPARISON OF FIRST AND SECOND PBI REPORTS IN 120 UNTREATED PATIENTS

Difference between first and second reports	Low, 0–7 μg.	High, 7.1–20 μg.
	No. of cases	No. of cases
0.0–1.0 μg.	34	24
1.1–2.0 μg.	19	13
2.1–3.0 μg.	6	9
3.1–4.0 μg.	1	9
4.1– —μg.	0	5
Total	60	60

the drawing of the blood samples; no specific thyroid treatment had been given. Some physiologic variation in the true blood level may have occurred in this interval so that the difference to some unknown extent may be due to this factor and not to laboratory error. In the high-level group this would be particularly likely, as these patients had active hyperthyroidism, which is characterized by spontaneous variations in intensity. In the low-level group 88.3 per cent agreed within 2.0 micrograms; in the high-level group, change in the disease itself seems to be indicated by large differences in about one third of the cases.

Effect of iodine medication and organic iodine compounds used in X-ray diagnosis

Inorganic iodine medication such as Lugol's solution disturbs the test grossly; this may be the fault of inadequate washing of the precipitate. Falsely high levels may persist a week after cessation of such iodine therapy.

Diagnostic roentgenographic dyes containing iodine remain in the blood for weeks, giving high PBI values that are not due to hyperthyroidism. This condition can be disclosed, in case of uncertain history, by the

fact that the I^{131} per cent tracer-dose uptake in twenty-four hours is characteristic of hypothyroidism, *i.e.*, blocked by the medication, whereas, if the elevated PBI were due to hyperthyroidism the uptake would be at least thirty per cent. The longest duration of artificial elevation of the PBI found after intravenous urography was four weeks; after bronchography nine months; after myelography, three years; and after cholecystography, three months.

In addition to the roentgenographic dyes, an iodine-containing amoebicide taken by mouth was found to cause elevation of the blood iodine in one case. The antithyroid drug, sodium 5-iodo-thiouracil, also raises the blood iodine levels markedly and renders the test, as used here, valueless for gauging such therapy.

ROUTINE INITIAL BLOOD PROTEIN-BOUND IODINE LEVELS IN VARIOUS STATES OF HEALTH

Effect of meals, exercise and delay in performance of the determination

A study was made of a group of 5 apparently healthy medical students. It is of importance to see if the test for blood iodine is deranged to a significant extent by mild exercise or by meals. Table 3 shows the results in this group. It seems apparent that there is no consistent effect noted from exercise (pedaling a stationary bicycle at 20 mph for fifteen minutes) or from meals. A meal high in fat or heavily contaminated with iodine would probably be a different matter. A 48-hour delay in analysis, with the blood stored at room temperature caused no significant change.

Studies on normal subjects

The histogram of the initial iodine assays of 100 assumed normal subjects is shown in Figure 1a. These results are part of a series to be presented by one of the authors (A.L.C.) in a later study. The range in this group is from 4 micrograms per cent to 8.5 micrograms per cent, with a mean of 5.5 micrograms per cent. These figures suggest a logarithmic rather than arithmetic distribution; analysis of the data gives a log mean of 0.7354 ± 06824.

$$X = 0.7354 \pm 1.285 = 0.8225 \text{ or } 0.6483.$$
$$0.7354 \pm 2.335 = 0.8944 \text{ or } 0.5764.$$

As a basis for comparison with future groups, it may then be assumed, after conversion of the above figures, that 90 per cent of our normal subjects will show levels above 4.45 micrograms per cent or below 6.65 micrograms per cent; and that 99 per cent will show levels above 3.77 micrograms per cent or below 7.84 micrograms per cent.

As a corollary, Figure 1b shows the results of 90 assays performed on 5

healthy medical students. The range is from 4 to 8.5 with an isolated assay of 10.7; and the mean of this series is 6.2.

Figure 1c shows the histogram of 28 tests done on one individual. The range here is from 4 to 8.5 micrograms per cent with a mean of 6.2 micrograms per cent.

TABLE 3. EFFECT OF EXERCISE, MEALS, AND DELAY IN ANALYSIS, ON PBI

Student	Before	Immed. after	1 Hour after
		Exercise	
1	6.5	6.3	5.8
2	6.1	6.0	7.6
3	4.5	—	6.9
4	5.8	6.2	4.8
5	6.2	5.7	5.5
		Meals	
1	6.8	6.8	6.3
2	4.2	5.0	6.4
3	5.4	5.9	6.1
4	5.8	4.4	5.4
5	6.3	5.1	5.1
		48-hour delay in analysis	
	Immediate		After 48 hrs.
1	7.3		5.9
2	5.4		7.1
3	5.1		4.9
4	6.2		5.8
5	6.6		6.5
6	7.0		5.5

ROUTINE INITIAL PBI DETERMINATIONS IN VARIOUS DISEASE STATES WHICH MAY AFFECT THYROID FUNCTION

The tabulations presented were made from the first protein-bound blood iodine reported in the hospital chart without regard to repetition. The diagnosis used is the final record room classification. *The objective of this analysis is not to prove the characteristic of any disease state but to reveal the variability of the method in clinical use.*

Hypothyroidism

The distribution curve of the initial iodine assays of 39 untreated pa-

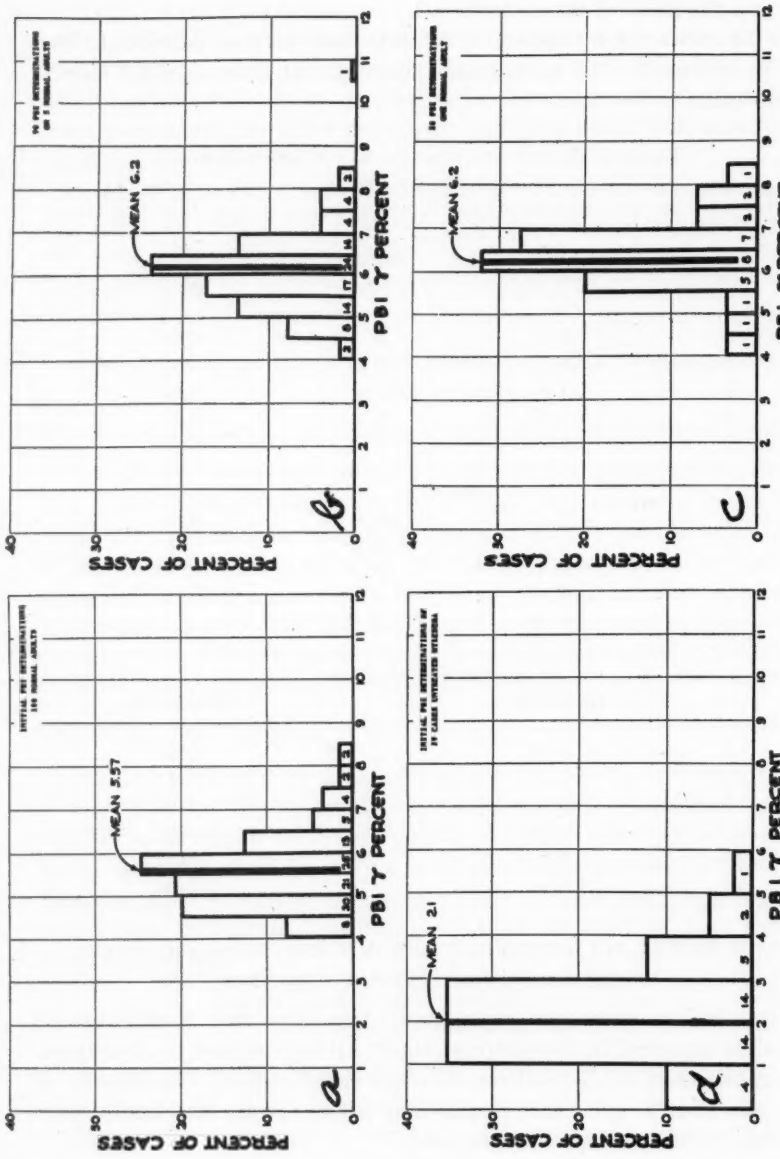

FIG. 1. a) Initial PBI determinations on 100 normal adults. b) 90 PBI determinations on 5 normal adults. c) 28 PBI determinations on 1 normal adult. d) Initial PBI determinations on 39 patients with untreated myxedema.

tients with myxedema (Fig. 1d) has a mean value of 2.1 micrograms per cent. Thirty-six of the 39 cases have initial values below 4 micrograms per cent, and 32 of the cases are below 3 micrograms per cent; the highest initial determination is 5.3 micrograms per cent. Any gross scattering due to laboratory error would have been demonstrated in this particular group which should have a narrow zone of true values due to the biochemical characteristics of hypothyroidism. The analysis shows that 84.6 per cent of these single assays are below 3 micrograms per cent, and 92.3 per cent are below 4 micrograms per cent.

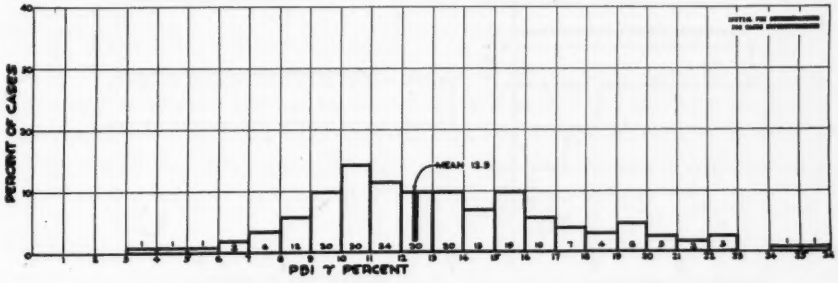

FIG. 2. Hyperthyroidism. Initial assay of PBI in 208 proven cases.

Hyperthyroidism

An average value of 12.3 micrograms per cent is obtained in the distribution diagram of initial iodine assays from 208 cases of hyperthyroidism (Fig. 2). The lowest level in this group is 3.5 micrograms per cent; and 5 cases, or about 2.5 per cent of the entire group, have initial iodine levels below 7 gamma per cent. If the patients with reported values above 7 gamma per cent actually had hyperthyroidism, such an analysis would indicate a 97.5 per cent clinical reliability of one determination; if the dividing line is 8 gamma per cent, the reliability is still 94.5 per cent; and if determinations above 9 gamma per cent are correct, *i.e.*, correspond with the actual disease state, and all those below are in error, which seems unlikely, the single determination would have a reliability of 89.0 per cent. The exact level of assays over 20 micrograms per cent is frequently not determined; such high results are often reported as "over 20," or "over 25"; in such instances the case has been placed in the "20" or "25" category.

Heart failure

Blood iodine assays are performed as part of the study of many cases of congestive heart failure of obscure etiology. Frequently cases of concomi-

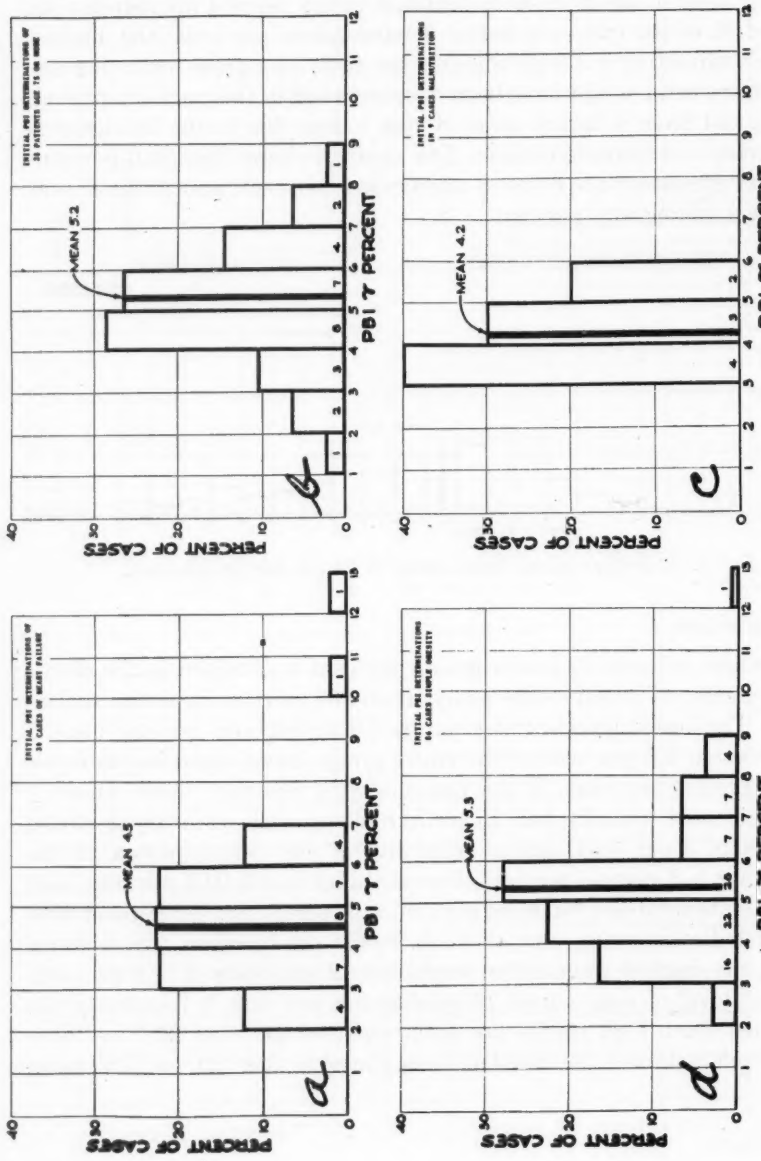

FIG. 3. a) Initial PBI determinations in 30 cases of heart failure. b) Initial PBI determinations in 28 patients aged 75 or more. c) Initial PBI determinations in 9 cases of malnutrition. d) Initial PBI determinations in 86 cases of simple obesity.

tant hyperthyroidism or hypothyroidism are uncovered. The 30 cases shown in Figure 3a are patients with congestive failure who did not have, upon follow-up studies, evidence of thyroid disease, and who had received no mercurial diuretics. Two cases of simultaneous hyperthyroidism in congestive heart failure are shown at 10 and 12 micrograms per cent. Because of the therapeutic implications of thyroid disease in heart failure, it is important to know if protein-bound iodine levels are disturbed by heart failure per se. The range is from 2 to 7 micrograms per cent, with a mean of 4.5. In comparison with the group of normal subjects, there seem to be more low iodine valués in the heart failure patients.

Senescence

Figure 3b shows the distribution curve of 28 patients aged 75 or more; there is no selection here as to sex or disease except to eliminate instances of hyperthyroidism and hypothyroidism. The range is from 1 to 9, with a mean of 5.2. Apparently old age need not be associated with lowered thyroid function as measured by the protein-bound iodine.

Malnutrition

It seems reasonable to suppose that the thyroid would share in any process of general undernutrition and perhaps manufacture less hormone. Figure 3c shows a distribution curve of 9 patients with severe malnutrition; none of the patients had thyroid disease and all were extremely thin and cachectic. The range of the PBI in these patients is from 3 to 6 micrograms per cent, with a mean of 4.2. More than half the cases are in the so-called normal range and there are no cases with iodine values above 6 micrograms per cent. This may indicate some depression of thyroid function.

Obesity

Figure 3d shows the distribution of initial iodine assays in 86 cases of "simple obesity." There was no evident metabolic disease in these patients other than obesity. The range is from 2 to 9 micrograms per cent, with an isolated level of 12.5. The mean is 5.3 micrograms per cent.

Nontoxic thyroid disease (simple goiters, solitary nodules, carcinoma, etc.)

The initial iodine determinations in 166 such cases show a wide range from 1 to 12.2 micrograms per cent (Fig. 4a). Approximately 74 per cent of the values fall between 4 and 8 micrograms per cent, and the average for the entire group is 5.9 micrograms per cent. This suggests that there may have been 11.4 per cent of the patients that actually had hyperthyroidism and 14 per cent that had hypothyroidism.

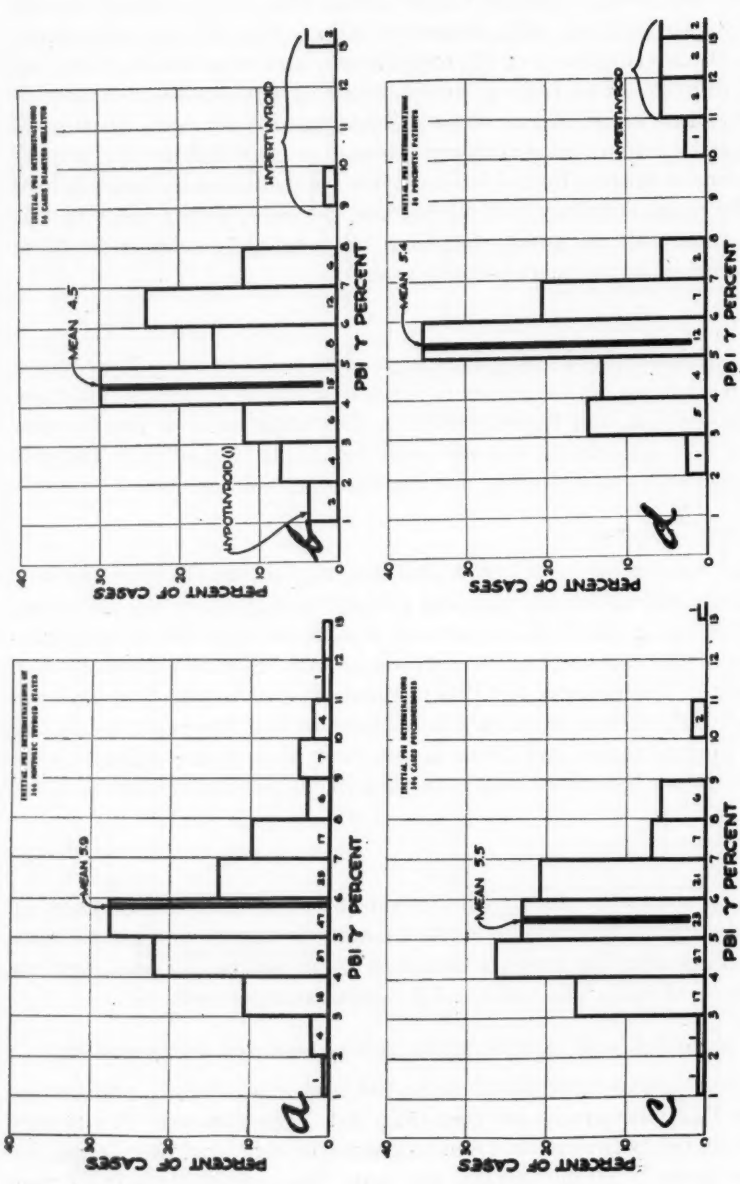

FIG. 4. a) Initial PBI determinations in 166 nontoxic thyroid states. b) Initial PBI determinations in 56 cases of diabetes mellitus. c) Initial PBI determinations in 106 cases of psychoneurosis. d) Initial PBI determinations in 38 psychotic patients.

Diabetes mellitus

Fifty-six cases of diabetes are plotted in Figure 4b. This group includes 3 cases of hyperthyroidism and 1 of myxedema as indicated in the figure. The range, exclusive of these, is from 1.9 to 8 micrograms per cent with a mean of 4.5 gamma per cent. About 73 per cent of the values in this group lie between 4 and 8 micrograms per cent.

Psychoneurosis

A group of 106 tense, anxious patients who presented symptoms which led to the use of a diagnostic iodine assay are shown in Figure 4c. None of the patients in this group was later diagnosed as having hyperthyroidism or hypothyroidism. Seventy-one per cent of the assays are between 4 and 7 micrograms per cent; 19 of the cases, or 18 per cent, are below 4 micrograms per cent in the initial assay. In the light of our present experience, it seems likely that the 3 patients with values above 10 did have hyperthyroidism.

Psychosis

Thirty-eight disturbed patients were studied. Six hyperthyroid patients were found among them, as indicated in Figure 4d. The range of values in the remainder is from 2 to 8 micrograms per cent, with a mean of 5.4 micrograms per cent.

Adrenal insufficiency

Four cases of frank Addison's disease were tested for levels of protein-bound blood iodine and showed values of 4.5, 5.0, 3.6 and 4.6 micrograms per cent, respectively.

Miscellaneous

Initial protein-bound iodine values were collected from the charts of 327 miscellaneous patients who were not finally proven to have either hypothyroidism or hyperthyroidism. In many cases further study was not carried out, even when the PBI was reported to be abnormal, as was true in about 10 per cent of the values above 7 gamma per cent and in about 22 per cent of those below 4 gamma per cent.

DISTRIBUTION ANALYSIS

Certain things can be noted upon comparing the distribution of the values in these various disease states with the limits found in the 100 normal subjects, *i.e.*, 99 per cent of the values were above 3.77 micrograms per cent or below 7.84 micrograms per cent. The wider range of initial iodine assays in the hospital patients is immediately apparent. In Table 4

TABLE 4. COMPARISON OF VALUES IN DISEASE STATES STUDIED, WITH 1% AND 10% LEVELS FOUND IN THE NORMAL GROUPS

	Under		*Over*	
	3.77 Micrograms per cent	4.45 Micrograms per cent	6.65 Micrograms per cent	7.84 Micrograms per cent
	1%	10%	10%	1%
Normal subjects (100)	(0)	(8)	(12)	(2)
Hyperthyroidism (208)	0.5% (1)	0.5% (1)	97.5% (203)	94.4% (196)
Hypothyroidism (39)	87.1% (34)	92.3% (36)	0% (0)	0% (0)
Obesity (86)	13.9% (12)	33.7% (29)	13.9% (12)	6.9% (6)
Malnutrition (9)	44.4% (4)	77.7% (7)	0% (0)	0 0
Senescence (28)	14.3% (4)	28.5% (8)	17.8% (5)	7.1% (2)
Nontoxic thyroid disease (146)	12.3% (18)	23.2% (34)	26.7% (39)	13.7% (20)
Psychoneurosis (89)	19.1% (17)	33.7% (30)	21.3% (19)	6.7% (6)
Diabetes mellitus (53)	16.9% (9)	37.7% (20)	18.8% (10)	5.6% (3)
Psychosis (30)	6.6% (2)	13.2% (4)	16.6% (5)	6.6% (2)
Heart failure (30)	36.6% (11)			6.6% (2)

is shown a comparison, by disease states, of the numbers and percentages of values above and below the 1 per cent and the 10 per cent levels in the normal subjects. In this table the figure 3.77 micrograms per cent represents that level below which 1 per cent of the values would occur in our nor-

mal subjects; 4.45 micrograms per cent is the level below which 10 per cent would occur. Similarly 6.65 micrograms per cent is the level above which 10 per cent of the values in our normal subjects might be expected to occur; and 7.84 micrograms per cent the level above which 1 per cent of values might be found. In contrast, of the hyperthyroid group, 97.5 per cent are values above 6.65 micrograms per cent; and of the hypothyroid group, 92.3 per cent are values below 4.45 micrograms per cent.

The groups of obesity, senescence, nontoxic thyroid disease, and psychoneurosis are similar to each other, with an appreciable number of cases above and below the normal divisions. There is probably a greater chance for technical error in these groups than in the "special study" normal subjects; this, however, does not seem sufficient to account for all such cases. One would conjecture that in these disease states there may have been instances of disturbed thyroid function that were overlooked, perhaps because the effects of such disturbed function do not fit our preconceived notions of hypothyroidism and hyperthyroidism.

Two groups—malnutrition (9 cases) and heart failure (30 cases)—show a large percentage of values below 4.0 micrograms per cent. Although the levels are not as low as in patients with myxedema, it appears that there is a definite lowering of protein-bound iodine in these two groups as compared with the normal subjects. The average value of these two groups, however, remains within the normal range. It would be of interest to compare other tests of thyroid function, such as radioiodine pickup, in an attempt to determine if there is any difference in the mechanism for the lowering of the protein-bound iodine in such groups, *e.g.*, underproduction or increased utilization.

DISCUSSION

The purpose in presenting this material is to evaluate the practicability of protein-bound blood iodine determinations when done on a large scale. The accuracy shown is satisfactory and compares favorably with that reported by Belk and Sunderman for other clinical chemical analyses (6). It should be pointed out that the procedure needs the supervision of a chemist, since contamination of supplies, variable potency of reagents, and mechanical errors in distillation and reading may occur. With such considerations in mind, the test has been found entirely adequate as a means of diagnosis for hyperthyroidism or hypothyroidism, and as a means of following the course of hyperthyroidism during treatment. Indeed, it is the senior author's personal opinion that this chemical determination will disclose instances of thyroid disease usually unrecognized and that the routine use of the PBI determination on the wards is well warranted by the clinical results, *i.e.*, by the demonstration of thyroid disease frequently missed.

SUMMARY

1. Agreement within 2.0 micrograms per cent was found in 96.6 per cent of 147 pairs of simultaneous determinations.

2. Agreement within 2.0 micrograms per cent was found in 88.3 per cent of 60 pairs of first and second reports in patients with normal or subnormal blood values, *i.e.*, those in which the fluctuation due to hyperthyroidism was probably not present.

3. Limited exercise, food, or a forty-eight hour delay in analysis have no detectable influence on the determination.

4. Artifacts which seriously impair the test are iodine medication and organic iodine dyes.

5. Typical distribution charts of results of PBI determinations in 100 normal adults, 39 patients with myxedema, 208 cases of hyperthyroidism, 32 with heart failure, 28 senile patients, 9 with malnutrition, 86 with obesity, 166 with nontoxic thyroid disease, 56 with diabetes mellitus, 106 with psychoneurosis, 38 psychotic patients, and 307 miscellaneous patients are shown.

6. In hyperthyroidism, 94.4 per cent of results are above the upper value beyond which lie only 1 per cent of normal values.

7. In hypothyroidism 87.1 per cent of results are below the lower value below which lie only 1 per cent of normal values.

8. In nonthyroid disease such as simple obesity, heart failure, psychoneuroses, psychoses, diabetes, senility, and malnutrition the means of the groups are not significantly different from the means of the normal groups.

CONCLUSION

Clinical experience with the blood protein-bound iodine determination used as a routine hospital procedure indicates its reliability and diagnostic value.

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AN ANALYSIS OF THE MEDICAL TREATMENT OF HYPERTHYROIDISM WITH THIOUREA AND IODINE: WITH SPECIAL REFERENCE TO THE BEHAVIOR OF THE SERUM PRECIPITABLE IODINE DURING THERAPY*

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DURING the past four years thiourea together with strong solution of iodine (Lugol's solution) has been used in the prolonged medical treatment of 139 patients with hyperthyroidism. Analysis of the usefulness of these agents in certain of these cases has already been made in preliminary reports from this department (1, 2). For a period, all patients with hyperthyroidism of whatever nature were treated with these drugs. Since a similar group is now being treated with propyl thiouracil, for comparison, it seems pertinent to summarize the information derived from the study of patients treated for long periods with thiourea. The development of this mode of therapy with thiourea in preference to other thyroid-depressant drugs has been discussed (2).

In addition to the basal metabolic rate, changes in weight and pulse rate, and other clinical manifestations of the disease, the concentration of the precipitable iodine in the serum (SPI) has been used in evaluating the condition of the patients during the course of therapy. The value of the SPI in establishing the existence of hyperthyroidism has been demonstrated (3, 4, 5). Since the concentration of the SPI is more immediately concerned with thyroidal activity than with the ultimate effects of the thyroid hormone as measured by the basal metabolic rate and clinical manifestations, a study of its behavior during the course of the disease has not only added precision to the analysis of the patient's response to various therapeutic measures, but has also clarified certain aspects of the course of hyperthyroidism. The initial response of the basal metabolic rate, heart rate and weight to the administration of iodine and other thy-

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roid-depressant drugs has been surveyed by others (6, 7). In this study particular emphasis will be given to the behavior of the SPI during the initial phase of therapy, during prolonged therapy, and during relapses of the disease after one or more of the drugs had been discontinued. Though these data on SPI were derived during the study of thiourea, the findings are equally pertinent to other thyroid-depressant drugs related to thiourea. The effectiveness and results of treatment will also be analyzed. The incidence and nature of certain possible toxic reactions to thiourea have been reported (8).

MATERIALS AND METHODS

The diagnosis of hyperthyroidism was firmly established in all of the 139 patients by several means. All of the patients had unmistakable signs and symptoms of hyperthyroidism, all had increased basal metabolic rates and all had increased SPI. Furthermore, all improved to variable degrees while under medical management. Thiourea was given to an additional 21 patients suspected of having thyrotoxicosis. These cases are not included in this study since in some, after further observation, the original diagnosis appeared to be questionable and in others, concomitant disorders, such as congestive heart failure, were so severe and complex that an adequate analysis of the effectiveness of treatment was impossible. Three types of initial therapy were used. Though 21 patients were started on strong solution of iodine alone and 18 on thiourea alone, the remaining majority were started on thiourea in small, moderate or large doses concomitantly with strong solution of iodine. The daily dose of the latter was 15 drops per day. During the period of prolonged, continuous treatment almost all of the patients received both thiourea and strong solution of iodine. The general clinical state of the patient, SPI, basal metabolic rate, body weight and pulse rate were recorded periodically throughout the time of observation. The SPI was determined by the method of Riggs and Man (3, 9). The normal range for adults varies between 3.8 and 7.9 micrograms per cent.

Composition of the group. Table 1 summarizes certain characteristics of the 139 patients. The initial basal metabolic rate varied from plus 5 per cent to plus 87 per cent. Similarly the range of the initial SPI was from 8.0 micrograms to 30.2 micrograms per 100 ml. of serum. The ratio of female patients to males was 3.5. Somewhat less than one third of the individuals had exophthalmos. There were 116 cases (84 per cent) of previously untreated hyperthyroidism; 23 cases (16 per cent) had had a relapse at various intervals of time following previous subtotal thyroidectomy. In 25 individuals the goiter appeared one or more years prior to any manifestation of hyperthyroidism and in 49 the goiter and evidences of overactivity of the gland definitely occurred simultaneously. In the remaining 65 in-

stances no conclusion could be reached concerning the time sequence. Thus in many, but not all, the thyroid gland enlarged with the onset of toxicity.

The number of cases in each decade of life is given in Table 2. The arithmetic average age of the group was 44.6 years. The goiter was stated to be diffuse in 60 per cent of the instances and a few of the nodular goiters

TABLE 1. COMPOSITION OF GROUP

Number of patients who received thiourea	160	
Number of patients excluded because of dubious diagnosis of hyperthyroidism	21	
Number of patients under consideration	139	
Females		109
Males		30
Exophthalmos present		31
Age range	7 to 75 years	
Number of untreated cases of hyperthyroidism		116
Number that had relapsed after thyroidectomy		23
Duration of surgical remission:		
Range: 1 mo. to 26 years		
Average: 9 years		
Time of onset of goiter in relation to hyperthyroidism:		
Number of patients in whom goiter appeared before hyperthyroidism (interval: 1 to 35 years)		25
Diffuse goiter	17	
Adenomatous goiter	8	
Number of patients in whom goiter and hyperthyroidism appeared simultaneously		49
Number of patients in whom relationship was unknown		65
Number of patients with complicating diseases (40 per cent of total)		55

were considered to be solitary adenomas. Eighty-four patients (60 per cent) had uncomplicated thyrotoxicosis, the remaining 55 suffered from a variety of complicating disorders. Hypertensive or arteriosclerotic cardiovascular disease accounted for most of these associated disorders (38 patients). A few individuals suffered from rheumatic heart disease, severe diabetes, chronic pulmonary disease, pernicious anemia, or carcinoma in addition to hyperthyroidism. Also, thiourea was used for variable intervals in 7 thyrotoxic pregnant women.

RESULTS

The concentration of the SPI during initial therapy. For analysis of the initial response, 101 of the patients were divided into seven groups according to whether they initially received strong solution of iodine alone, small,

TABLE 2. DISTRIBUTION OF CASES ACCORDING TO AGE OF PATIENT

Age in years	Number of patients
0–9	1
10–19	3
20–29	20
30–39	31
40–49	23
50–59	35
60–69	19
70–79	5
Unknown	2
Average 44.6 years	

moderate and large doses of thiourea in conjunction with strong solution of iodine, or solely large doses of thiourea. Pertinent characteristics of the members of each group are summarized in Table 3. The groups are similar in composition so far as the initial severity of the disease, the type of goiter, and the age and sex of the patients are concerned. Therefore, it is possible to assay and compare the response to the different therapeutic regimens.

The average concentration of the SPI at each interval of time was calculated for all the members of each group. These averages are shown in

TABLE 3. CHARACTERISTICS OF THE VARIOUS GROUPS OF THYROTOXIC PATIENTS TREATED INITIALLY UNDER DIFFERENT REGIMENS

Initial therapy*	Number of patients			Age in years (range)	Initial (average)		Type of thyroid disease		
	Total	Female	Male		Serum ppt. iodine, micrograms %	BMR %	Grave's	Toxic adenoma	Unclassified hyperthyroidism
Lugol's solution alone	21	15	6	18–68	11.3	+34	13	1	7
10-15-25 mg. thiourea, plus Lugol's	18	14	4	7–64	11.7	+35	13	1	4
50 mg. thiourea, plus Lugol's	15	14	1	20–71	13.7	+48	6	2	7
70–75 mg. thiourea, plus Lugol's	14	11	3	23–69	11.5	+45	8	1	5
140–150 mg. thiourea, plus Lugol's	10	7	3	25–60	12.6	+39	5	2	3
210 mg. thiourea, plus Lugol's	11	7	4	28–69	14.8	+44	8	1	2
210 mg. thiourea alone	12	8	4	30–67	13.3	+40	5	1	6

* The patients received the indicated medications in daily, divided doses. The majority of the patients that received Lugol's solution (strong solution of iodine, U.S.P.), alone or in conjunction with thiourea, received 15 minims per day; a few received 10 minims per day.

Figure 1. The rate and extent of fall in the concentration of SPI is similar whether strong solution of iodine alone is used or whether small or moderate doses of thiourea are given in addition. When the dose of thiourea exceeds 200 milligrams a day, however, the SPI falls somewhat more promptly and to a lower average level, whether iodine solution is administered simultaneously or not. Hence, the initial effect on the SPI of small doses of thiourea is probably masked by the greater effect of the iodine solution. That

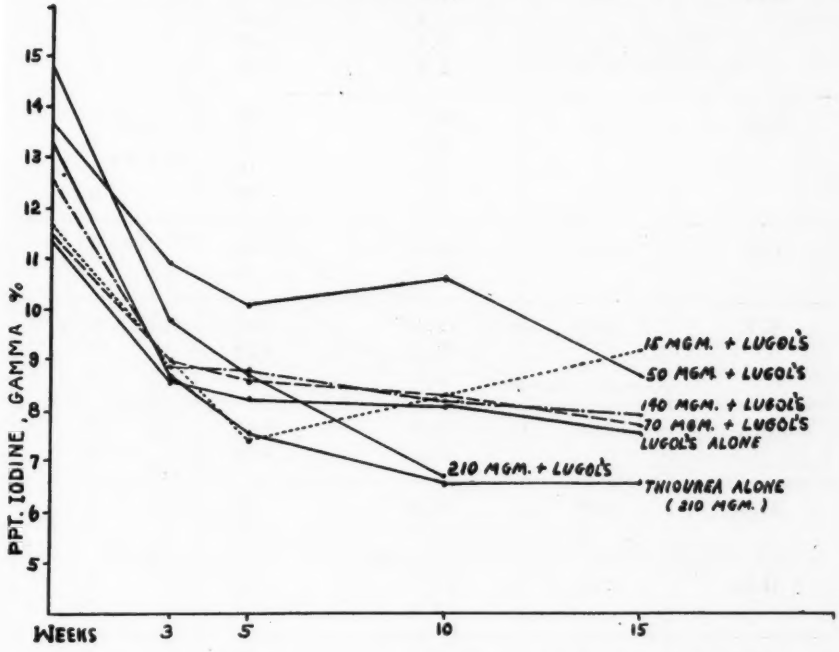

FIG. 1. The initial average response of the serum precipitable iodine of 101 thyrotoxic patients treated with iodine solution alone and with iodine and thiourea in combination.

the more profound depression of the SPI by large doses of thiourea is merely a function of the amount of drug given, is indicated by the fact that the addition of strong solution of iodine did not alter the rate or extent of fall of the SPI. Large doses of thiourea, therefore, will mask any effect of iodine solution on the SPI. Thus, neither an additive effect nor interference with the thyroid-depressant function of one drug, when both are given, is demonstrated in the initial response to therapy.

In Figure 2 the course of the SPI is compared with that of the basal metabolic rate following the administration of more than 200 mg. of thiou-

TABLE 4. THE RESPONSE OF THE BMR AND SPI TO LARGE DOSES OF THYROID-DEPRESSANT DRUGS

Patient	Dose of thiourea	Serum precipitable iodine	Basal metabolic rate	Duration of treatment
	mg./day	micrograms %	%	weeks
J.H.	400	11.4	+61	0
		7.2	+55	½
		6.3	+22	3
		2.9	+26	7
K.S.	300	10.6	+36	0
		3.3	− 1	2½
		2.5	−19	5
		2.4	−26	9
L.J.	210	10.9	+26	0
		3.6	− 3	4½
K.F.	140	12.5	+48	0
		3.2	+24	4
		2.7	+ 4	8
M.K.	210	8.9	+44	0
		7.6	+19	3
M.M.	210	10.3	+34	0
		6.4	+16	3
H.M.	210	12.7	+54	0
		4.3	− 1	7½
J.N.	210	8.3	+24	0
		7.1	+26	3
		5.8	+30	7
M.P.	210	11.6	+54	0
		6.4	+27	4
C.V.	280	10.5	+18	
		8.1	+26	8½
G.W.	210	17.0	+48	0
		6.1	+ 6	3
		7.1	+10	7
M.W.		30.2	+87	0
		8.0	+54	6

rea daily as initial therapy. The SPI falls more precipitously. Because of this discrepancy in rate of response, a temporary dissociation between metabolic rate and blood iodine may be observed. This phenomenon is more clearly demonstrated by examination of individual cases. The response of the SPI and basal metabolic rate of 12 patients given large doses of thiourea is shown in Table 4. It is noted that in 9 patients, when the

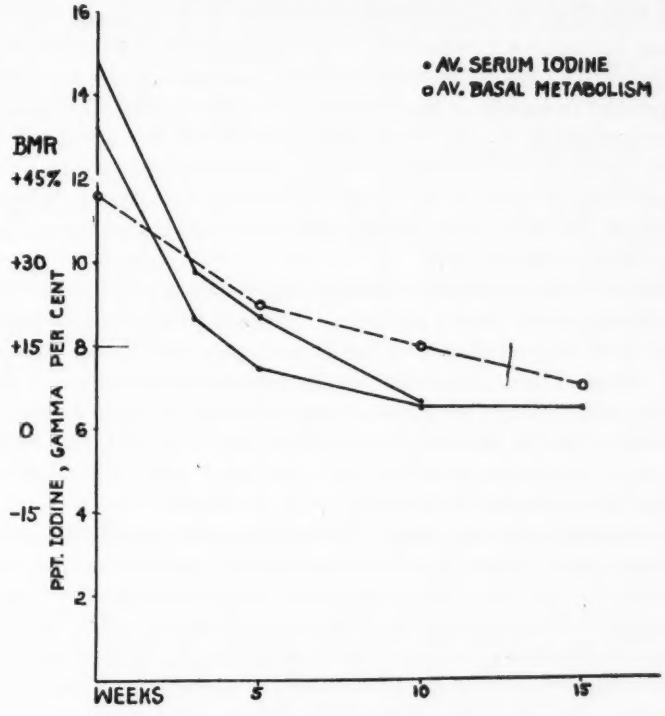

FIG. 2. A comparison of the average rates of fall of the SPI and basal metabolic rate of thyrotoxic patients treated with large doses of thiourea.

first normal SPI was obtained, the basal metabolic rate was still elevated above plus 15 per cent in 7 of them and was normal in 2. In 4 patients when the first subnormal SPI was obtained, the basal metabolic rate was still above plus 15 per cent in 2 of them and was normal in 2. Thus, in Case K. S. the SPI fell to subnormal levels while the basal metabolic rate had fallen only to the normal range and she was not clinically myxedematous. However, when the same dose of thiourea was continued for an additional period, the metabolic rate continued to fall and outspoken myxedema de-

veloped. It may be recalled that similar dissociation between SPI and metabolic rate has been observed after subtotal thyroidectomy (10) and following discontinuance of exogenous thyroid medication in euthyroid subjects (11) if determinations of the SPI and basal metabolic rate were made at frequent intervals. Also, Williams (10) described a similar lag in the fall of the basal metabolic rate as compared to the SPI in 1 patient receiving thiouracil. Thus, when the SPI is falling from high levels, appreciable time may be required before changes in the concentration of the circulating hormone are reflected in the appearance of functional abnormality. Either the tissues contain residual amounts of the hormone previously present in excess, or for a period are able to utilize the diminishing available hormone in a more economical fashion. In any event the finding of an abnormally low SPI during the early weeks of therapy with a thyroid-depressant drug, in spite of the absence of clinical myxedema, is indicative of overdosage. The SPI more quickly reflects altered thyroid secretion than does the basal metabolic rate.

The control of hyperthyroidism during prolonged use of thiourea. The dose of thiourea employed during prolonged treatment varied according to the changing needs of the patient. Of the 139 patients only 8 were treated with thiourea alone. The therapeutic results achieved with different doses of iodine with and without thiourea are summarized in Table 5. The disease was considered to be definitely controlled when the SPI was within the normal range, the basal metabolic rate was below plus 15 per cent and/or when there were no clinical evidences of an abnormal thyroid state beyond residual exophthalmos and goiter. The disease was considered to be definitely uncontrolled when the SPI exceeded 8.0 micrograms per cent, the basal metabolic rate was higher than plus 15 per cent and/or when there was clinical evidence of hyperthyroidism. Occasionally, when the evidence from these three methods of evaluation conflicted, the individuals could not be placed with certainty in either of these two categories. These results are listed as questionable. A few cases of the disease were considered to be controlled despite slight elevations of the SPI, if the basal metabolic rate was normal and there was no clinical evidence of thyroid dysfunction. A period of less than five weeks was considered too brief to allow evaluation of a particular therapeutic regimen.

Temporary myxedema was induced in 19 instances. This occurred only when the larger doses of thiourea were employed. Even though the symptoms of hypothyroidism that appear during these phases may rapidly be abolished by simply reducing the size of the dose, it is important to avoid such hypothyroid episodes because in 2 instances they were accompanied by a definite increase in the size of the goiter and in 2 other instances by an increase in exophthalmos. In this series, if symptoms of myxedema ap-

peared, either the size of the dose was promptly decreased or treatment with desiccated thyroid was begun (8 patients). The importance of preventing myxedema from persisting for any length of time has been stressed (2, 13).

Small doses of thiourea together with strong solution of iodine were only slightly more effective than the iodine solution alone. Larger doses

TABLE 5. EFFECTIVENESS OF DIFFERENT REGIMENS OF PROLONGED THERAPY*

Instances in which the following occurred	During therapy with Lugol's alone	During therapy with Lugol's plus thiourea, mg.					
		10–25	50	70–75	140–150	210	280 and over
Myxedema	0	0	1	6	4	1	7
Definite control of hyperthyroidism	14 (48%)	22 (51%)	18 (56%)	29 (70%)	20 (77%)	14 (75%)	4 (80%)
Definite lack of control of hyperthyroidism	15	21	15	15	7	5	3
Questionable result	5	14	8	20	11	15	7
Average time on drug in weeks	*25*	*21*	*31*	*24*	*20*	*19*	*22*

* The numbers in each column indicate the actual number of instances in which a particular therapeutic regimen was used to achieve a particular result. Many patients were maintained on different schedules of therapy at different times so that the number of instances involved exceeds the total number of patients. In this way the over-all effectiveness of the drugs was estimated. The percentages given in parentheses indicate the frequency whereby definite control, as compared to definite lack of control, was attained.

of thiourea caused a satisfactory remission of the disease in approximately 80 per cent of the cases. However, in spite of large doses a few patients remained hyperthyroid during the period of observation. In the doses used, thiourea is a moderately effective thyroid-depressant drug.

The fluctuant and persistent character of hyperthyroidism is apparent in the course of certain of the patients. In several, the disease was controlled at one time and uncontrolled at another despite the maintenance of constant doses of the drugs and the absence of any evidence of coexisting disease or complication. The effective dose must therefore be periodically altered according to the changing needs of the patient. In other words, so-called "maintenance" doses are not always constant in amount in the

same individual. Periodic examinations are, therefore, important.

In order to assess the value of combining thiourea and strong solution of iodine in the prolonged therapy of hyperthyroidism, individual cases are presented in Figure 3. On the upper portion of the figure are shown patients in whom the disease was controlled with small or moderate doses

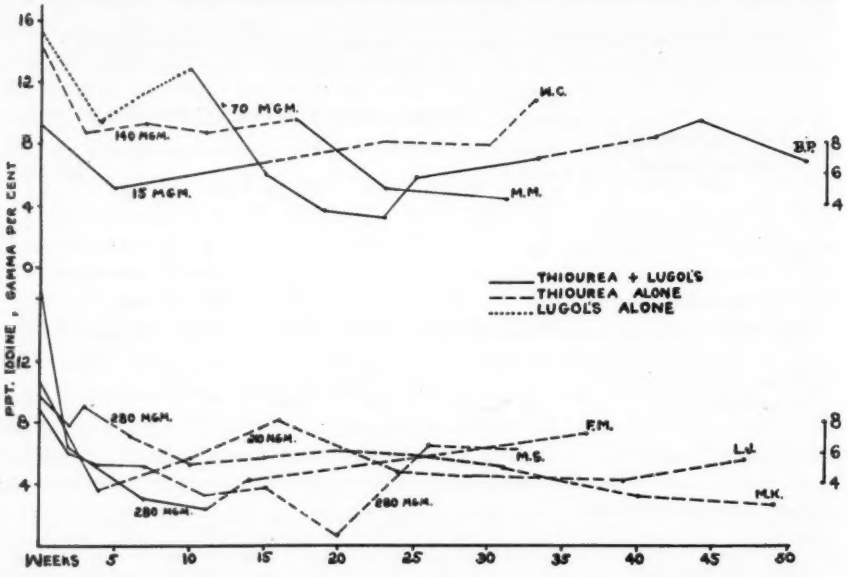

FIG. 3. In the upper portion of the figure are shown patients whose thyrotoxicosis was uncontrolled with small doses of thiourea alone or with iodine solution alone but whose disease was controlled when both drugs were administered in combination. In the lower portion are shown patients who received large doses of thiourea; these patients suffered no relapse of their hyperthyroidism in spite of the discontinuance of iodine solution.

of thiourea and strong solution of iodine and in whom it recurred when the iodine was discontinued. In 1 patient, B. P., hyperthyroidism was controlled again when the administration of iodine was resumed. In patient M. M. the disease was only partially controlled by thiourea alone but completely controlled when iodine was given in addition to the same amount of thiourea as before. In patients F. M., M. S., L. J. and M. K. amounts of thiourea in excess of 200 mg. per day were used. In these instances discontinuance of the iodine solution did not produce any noticeable change in the degree of control of the disease. If adequate amounts of thiourea are used, therefore, simultaneous iodine administration is unnecessary for the control of symptoms of glandular hyperactivity. However, the use of

iodine probably allows the employment of somewhat smaller doses of thiourea in some patients. In addition, iodine promotes involutionary changes in the affected thyroid gland and may protect the patient against exophthalmos.

The behavior of the SPI during prolonged medical therapy. In 119 of the 139 patients the SPI at many different times during prolonged treatment

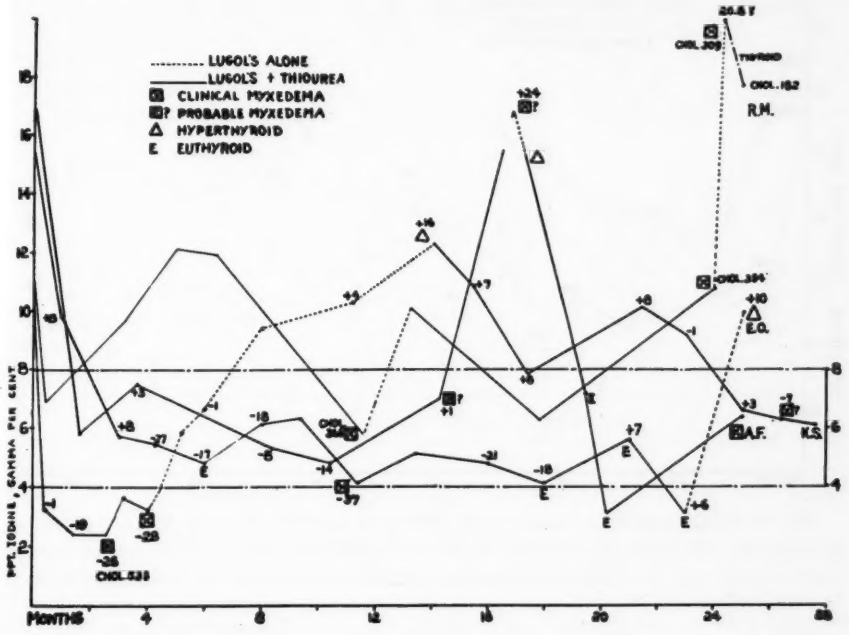

FIG. 4. Examples of the course of the SPI in certain unusual cases of hypothyroidism induced by medical therapy. In addition, the concomitant levels of the basal metabolic rate and total serum cholesterol (in mg. per 100 cc.) are recorded.

was entirely consistent with the clinical findings and basal metabolic rate. In 20 patients, however, the SPI could not in certain instances or over some periods be correlated with the apparent clinical condition of the patient. Certain of these exceptions need to be examined in order that the true significance of the SPI during prolonged therapy may be interpreted. In Figure 4 are shown certain instances of clinical hypothyroidism. In patient K. S. myxedema developed but patients A. F. and E. O. were euthyroid despite SPI's almost as low. However, in the 2 latter cases the SPI was depressed for only a short interval; in the case of K. S., the SPI was depressed for a longer period so that in about seven weeks myx-

edema became frankly manifest. That the average rate of fall of the basal metabolic rate is slower than the fall of the SPI during the initial phase of treatment of hyperthyroidism has already been noted. Following the development of subnormal levels of the SPI considerable time may intervene before clinical evidence of myxedema appears. On the other hand, there

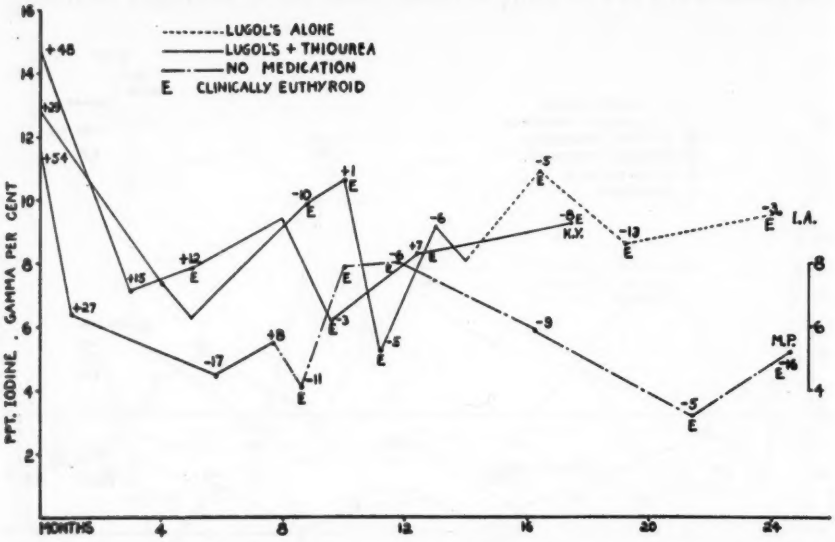

FIG. 5. Examples of the course of the SPI in 3 patients (I. A., K. Y. and M. P.) In I. A. and K. Y. the SPI remained elevated in spite of lack of evidence of hyperthyroidism. In M. P., are seen the wide fluctuations that the SPI may undergo in a previously hyperthyroid individual.

appears to be no lag in the appearance of hyperthyroidism after the SPI becomes elevated. In 9 patients who were studied at sufficiently frequent intervals and whose disease relapsed following discontinuance of thiourea, the rise of the SPI was almost simultaneously associated with an increase in the basal metabolic rate and with the appearance of clinical hyperthyroidism. This is in agreement with previous work wherein thyroxine or desiccated thyroid were administered to normal subjects (11, 14). Thus, these observations suggest that the SPI accurately portrays the degree of activity of the thyroid gland at any particular time. In overactivity the symptoms and signs of hyperthyroidism are prompt to appear, but in activity which decreases to a subnormal level there is an appreciable delay before symptoms of hypothyroidism appear. It seems as if the tissues still had a small supply of material that had to be dissipated before the lack of new thyroid hormone became manifest. This affords an explanation for

certain discrepanices between the SPI and the clinical manifestations of thyroid disease. In addition, however, there occur instances (such as for example R. M. and possibly A. F. (Fig. 4)) in which an elevated SPI is seen in conjunction with outspoken myxedema. Such inexplicable discrep-

TABLE 6. RESULT OF DISCONTINUANCE OF THIOUREA IN 22 PATIENTS CONTROLLED WITH THIOUREA AND LUGOL'S SOLUTION

	No. of patients	Duration of remission	
Relapse		*Range*	*Average*
while on Lugol's alone	7	1–11 mo.	3½ mo.
while on no medication	5	3–16 mo.	7 mo.
Total	12		
		Duration of follow-up	
No relapse		*Range*	*Average*
while on Lugol's alone	5	2–19 mo.	9 mo.
while on no medication	5	5–30 mo.	15 mo.
	10		
Result of thyroidectomy in 7 patients			
Relapse	0		
		Duration of follow-up	
No relapse		*Range*	*Average*
while on Lugol's alone	3*	4–18 mo.	10 mo.
while on no medication	4	9–52 mo.	28 mo.

* One patient has some regrowth of gland, but BMR was minus 15 per cent and last SPI, 7.6 gamma per cent.

ancies suggest the rare presence in the serum of a precipitable iodine which is not altogether composed of thyroid hormone. In a few other patients, moreover, the SPI remained moderately elevated in spite of normal basal metabolic rates and a clinically euthyroid state. These exceptional cases are shown in Figure 5. Whether this indicates the presence of an abnormal precipitable iodine or of some kind of tolerance by the tissues to increased circulating thyroid hormone is unknown. This problem is discussed in another publication (8). With these unusual exceptions, however, the SPI may be closely correlated with the state of the patient's disease and is the most sensitive criterion of therapy.

Results of discontinuance of thiourea. Thiourea was discontinued in 22 of

139 patients after the hyperthyroidism had been adequately controlled. The results are summarized in Table 6. In 12 instances relapse of the disease occurred. Seven of these patients continued to take strong solution of iodine but the disease recurred after an average time interval of three and a half months. In those who did not continue to take iodine, relapse occurred after an average interval of seven months. Because of the variability of the disease and the small numbers involved, no conclusions can be based

TABLE 7. CHARACTERISTICS OF THE PATIENTS IN WHOM THIOUREA WAS DISCONTINUED, COMPARED TO THE CHARACTERISTICS OF THOSE FEW MANAGED BY IODINE ALONE AND THOSE SURGICALLY TREATED

	Thiourea		Lugol's as only drug (8 patients)	Surgically treated (8 patients)
	Relapse (12 patients)	No relapse (10 patients)		
Size of gland	Small 2 Mod. 6 Large 3	Small 7 Mod. 3 Large 0	Small 6 Mod. 2 Large 0	Small 2 Mod. 4 Large 2
Initial SPI	av. 13.8 gamma % (range: 9.2–18.9)	av. 12.5 gamma % (range: 8.4–19.1)	av. 10.2 gamma % (range: 8.6–12.7)	av. 13.9 gamma % (range: 9.5–22.2)
Initial BMR	av. +41% (range: +24 to +56)	av. +40% (range: +29 to +54)	av. +42% (range: +10 to +47)	av. +40% (range: +26 to +54)
Duration of medical treatment prior to stopping drugs total average: 17 mos. (range: 2–38 mos.)		av. 15 mos. (range: 3–37 mos.)		
Duration of control prior to stopping drugs total average: 9 mos. (range: 2–21 mos.)		av. 10.5 mos. (range: 3–26 mos.)		
Number of patients				
diffuse goiter	11	8	5	7
nodular goiter	1	2	3	1
exophthalmos	4	3	2	3
males	3	3	2	2

upon this difference. Ten patients have experienced a sustained remission for as long as thirty months after the thiourea was discontinued; 5 of these are receiving daily doses of iodine solution. Additional time will be required to evaluate this group properly.

Eight patients had subtotal thyroidectomies. One patient has not been seen since operation but 7 have been followed for from four to fifty-two months. None of these patients has developed a relapse.

Significant data relative to the patients who discontinued thiourea, the patients who had a subtotal thyroidectomy and 8 patients who received strong solution of iodine without thiourea are given in Table 7. Though the patients receiving thiourea were quite similar in other respects, such as in

the initial severity of the disease, the duration of medical treatment, the age and sex of the individuals, relapse appears to occur more commonly in those with the large goiters. The patients who were successfully treated with iodine alone not only had a milder type of hyperthyroidism but also had smaller thyroid glands than did many of the members of the other groups. Thus far, no thyrotoxic patient with a large goiter has had a sus-

TABLE 8. PRESENT RESULTS ON ORIGINAL 139 CASES

Number still being followed 76	
Definite control of hyperthyroidism while on thiourea and/or iodine	38
Definite lack of control of hyperthyroidism while on thiourea	2
Definite control without medication	5
Questionable control while on thiourea	6
Followed after thyroidectomy	7
Changed to propylthiouracil	18
Number lost to clinic 63	
Reason unknown	39
Refused to return	2
Known to be followed by other physicians	8
Known to have had thyroidectomy elsewhere	5
Lost after thyroidectomy at NHH	1
Died	8
Died with hyperthyroidism: A.B., M.W., E.R., E.R., A.P., E.S.	
Died from other causes: E.K., G.F., M.G.	
Status of hyperthyroidism when last seen:	
Controlled 29	
Uncontrolled 18	
Questionable control 16	

tained remission after discontinuance of thiourea. It is conceivable that the size of the thyroid gland may be an important guide in determining the probable success of interrupting medical therapy.

Present status of the 139 patients. Pertinent data concerning the present status of the 139 patients studied are summarized in Table 8. A detailed report of the 5 patients who died while receiving thiourea and iodine for treatment of hyperthyroidism has already been published (8). Carcinoma of the jaw, carcinoma of the uterus and ulcerative colitis caused the death of 3 additional patients. Sixty-five patients ceased to attend the clinic after periods of treatment which extended for from one to forty-two months and which averaged 13.6 months. Though control of the hyperthyroidism of most of the patients who continued to attend the clinic proved to be possible by one therapeutic regimen or another, the fact that of those 65 patients who were lost to the study, 24 still had hyperthyroidism when they

were last seen is significant. Clearly, relatively prompt and adequate control of the disease is desirable if truly satisfactory results are to be achieved by medical treatment. The lack of definitiveness of prolonged medical treatment and the unsightliness of the goiter accounts for many of the decisions to discontinue the therapy.

DISCUSSION

Since the patients in this study were an unselected group and since they were categorically treated by medical therapy certain advantages and disadvantages of such therapy emerged. In general, there appeared to be no inherent disadvantage in treating all thyrotoxic patients, at least for a period, with thiourea. However, the indications for continued and prolonged medical management were more definite in certain thyrotoxic patients than in others. There was little question that this form of therapy was preferable to surgery in those individuals who were poor surgical risks because of old age and/or complicating disease. An important advantage of medical treatment over other methods of therapy resided in its flexibility. Undesirable changes consequent upon treatment, such as hypothyroidism, were easily reversed by altering the dose of the drug. Further, many of the consequences of thyroidectomy are not encountered with medical treatment, *e.g.*, permanent myxedema, laryngeal nerve palsy and parathyroid insufficiency. Since the frequency of these complications increases with subsequent thyroidectomies, prolonged medical management offers a satisfactory alternative for most patients with recurrent hyperthyroidism. The fact that 7 thyrotoxic women were satisfactorily carried through pregnancy by the use of thiourea and iodine solution indicates the usefulness of thyroid-depressant drugs in such cases.

It is recognized that in some patients the hyperthyroid state appears to be a spontaneously remittent disease. It is of greatest importance to identify these patients and to employ conservative medical measures to tide the patients over the active phase of their illness; more drastic measures, such as the use of surgery or radioactive iodine, could then be avoided. From this study and from other reports (7, 15, 16) it is apparent that patients with mild hyperthyroidism and small goiters are more likely to have a sustained remission after discontinuance of thyroid-depressant drugs than patients with more severe thyrotoxicosis and large goiters. A thorough trial of medical treatment is warranted in the former patients. However, if relapse occurs, the further employment of a thyroid-depressant drug as a continuous form of therapy becomes a more questionable procedure. This is especially true if the patient is young, has no complicating disease and suffers from primary hyperthyroidism. More definitive measures should then be considered. The high rate of relapse after discontinuance of

drug therapy comprises its chief disadvantage. Other undesirable features include occasional untoward reactions to the drug, occasional further enlargement of the goiter and the problem of frequent examinations necessitated by the nature of such therapy. However, careful, and sometimes frequent follow-up examinations are needed for those patients treated by surgery or radioactive iodine. In any event, it is clear from this study that the treatment of hyperthyroidism must be individualized. Rigid adherence to a general rule or system of therapy is neither wise nor necessary, especially since several forms of therapy are available to the thyrotoxic patient.

Behavior of the SPI during therapy. During the initial therapy of thyrotoxic patients, the extent and rate of fall in the concentration of the SPI was similar, whether strong solution of iodine alone was used or whether small or moderate doses of thiuorea (140 mg. or less per day) were given in addition. More profound depression of the SPI resulted when thiourea was administered in a dose of more than 200 mg., whether iodine solution was given simultaneously or not. Neither an additive effect nor definite interference with the thyroid-depressant function of one drug when both were given was demonstrated in the initial response to therapy.

When large doses of thiourea were used as initial therapy, the SPI fell more precipitously than did the basal metabolic rate. Because of this discrepancy in rate of response, a temporary dissociation between the metabolic rate and the SPI may be observed. Occasionally a subnormal SPI was noted while the basal metabolic rate was normal or even elevated. Thus, when the SPI is falling from high levels, appreciable time may be required before changes in the concentration of circulating hormone are reflected in the appearance of functional abnormality. On the other hand, no lag in the reappearance of hyperthyroidism was noted when the SPI became elevated. The finding of a subnormal SPI during therapy with a thyroid-depressant drug, in spite of the absence of clinical myxedema, is indicative of overdosage. It appears that the SPI more quickly reflects altered thyroid secretion than does the basal metabolic rate.

By following the SPI and the clinical state of the patient, the fluctuant and persistent character of the hyperthyroid state, during prolonged medical therapy, was apparent in some cases. In these, the disease was controlled at one time but uncontrolled at another, despite the administration of constant amounts of the drugs. Therefore, so-called "maintenance" doses of a thyroid-depressant drug are not always constant in amount in the same individual.

In a few patients the SPI became inexplicably elevated during prolonged therapy and its level could not be correlated with the clinical condition of the patient or the basal metabolic rate.

SUMMARY

A study is presented of the effects of medical treatment with thiourea and iodine in 139 hyperthyroid patients. Particular attention is paid to alterations in serum precipitable iodine (SPI). When large doses of thiourea were used as initial therapy, the SPI fell more precipitously than the BMR. This discrepancy in the rate of response may cause a temporary dissociation between the BMR and SPI. Appreciable time is required before the effects of low concentrations of circulating thyroid hormone are manifested by clinical hypothyroidism and by distinct depression of the BMR. The finding of a low SPI indicates overdosage with thyroid-depressant drug. Usually, no lag was observed in the appearance of thyrotoxic symptoms and signs used when the SPI became elevated. However, in a few instances the SPI became inexplicably elevated during continued therapy.

In general, there is no inherent disadvantage to treating all hyperthyroid patients, at least for a period, with thyroid-depressant drugs. Some of the advantages and disadvantages that emerged from this study of the medical management of hyperthyroidism are discussed. Although an important advantage of medical treatment resides in its flexibility, it is necessary to follow the patients carefully, since so-called "maintenance" doses of a thyroid-depressant drug are not always constant in amount in the same individual.

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THE TREATMENT OF EUTHYROID CARDIAC PATIENTS WITH INTRACTABLE ANGINA PECTORIS AND CONGESTIVE FAILURE WITH RADIOACTIVE IODINE*†

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THE possible relationship between disturbances of the thyroid gland and cardiac symptomatology has long been recognized. In 1825, Parry (1) clearly described the development of congestive failure and angina pectoris coincident with the development of the classic signs of exophthalmic goiter. He noted the subsidence of congestive failure with a decrease in size of an enlarged thyroid gland. Similar observations have been reported by Kocher (2) and Hamilton (3) (4). In 1924, Means (5) in discussing the treatment of cardiac dyspnea noted that "first of all comes treatment directed toward reduction of the metabolic rate. This is seen most strikingly in treatment by rest, particularly in heart failure. Mere confinement to bed, of course, makes total metabolism closely approach basal and therefore, greatly diminishes the work both of the heart and the respiratory organs and consequently the dyspnea . . . . In the dyspnea of hyperthyroidism . . . those measures which reduce the hyperthyroidism and therefore the metabolism by the same token diminish or abolish dyspnea."

Previous observations by Blumgart (6) showed that the velocity of blood flow was considerably slowed in patients with congestive heart failure and a normal basal metabolic rate; the retardation in the velocity of blood flow generally paralleled the degree of circulatory insufficiency. Measurements of the velocity of blood flow in patients with myxedema (7), in the absence of circulatory insufficiency or congestive heart failure, showed a degree of slowing similar to that observed in patients with congestive heart failure. It was therefore considered that "if the normal metabolic rate of the

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patient with congestive heart failure (or angina pectoris) were reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of his body" (8); the metabolic demands would be reduced to a level to conform to the blood supply.

Surgical total thyroidectomy. The validity of this hypothesis was confirmed by the results obtained following surgical total thyroidectomy and the consequent myxedema in over 350 patients with intractable angina pectoris or congestive failure operated upon in 26 different clinics (8, 9, 10). More than 50 per cent of the patients obtained distinct relief of angina pectoris or congestive heart failure and a definite correlation was observed between the reduction of the metabolic rate and clinical improvement. The magnitude of the surgical procedure in such seriously ill patients of whom many had an inevitable short life expectancy, militated, however, against the practicability of this method of treatment.

Medical total thyroidectomy. In 1933, Blumgart *et al.* (8), in describing the results following surgical thyroidectomy, noted that "it is hoped that ultimately operation will be unnecessary to produce a low metabolic rate." Following the demonstration of the therapeutic benefit of the thiourea derivatives in thyrotoxicosis, these compounds, including propylthiouracil have been utilized in euthyroid patients with angina pectoris or congestive failure in order to attain the hypometabolism of total thyroidectomy (11–18). Unfortunately, however, hypothyroidism can be induced in only some patients. Moreover, to maintain the hypothyroid state, administration of the drug must be continued for the remainder of the patient's life. At any time during such administration, dangerous drug reactions, including granulocytopenia, agranulocytosis and death may suddenly occur (19–25).

In this report, we present the results of our study of radioactive iodine (I^{131}) as an agent in the production of hypothyroidism, and its therapeutic effects in angina pectoris and congestive heart failure.

METHODS AND CLINICAL MATERIAL

Since November, 1947 (26–28) persistent hypothyroidism has been induced with one or more doses of radioactive iodine, I^{131}, in 23 of 29 patients with intractable and disabling angina pectoris or congestive heart failure. In the remaining 6, the period of observation following I^{131} has been too short for inclusion in this study.

The total oral dose of I^{131} administered to each patient has been from 25.5 to 176 millicuries[1] (average, 61.0). In 9 patients, a single dose of 25.5 to 42.5 millicuries (average, 31.5) was sufficient to induce hypothyroidism

[1] The activity of the millicurie used in this study is that of the U. S. Bureau of Standards.

or myxedema. In the remaining patients multiple doses were utilized: in 12 patients, two doses totalling 32.5 to 98.5 millicuries (average, 56); in 5 patients, three doses of 60.5 to 90 millicuries (average, 72.5), and in 1 patient each, four, five and six doses totalling 150, 176 and 129.5 millicuries respectively were administered.

The course of angina pectoris and congestive failure is often irregular and characterized by periods of unexpected exacerbation and remission. We have, therefore, selected only patients who, despite marked restriction of activities for many months or years, showed evidence of continued incapacity after having received all standard forms of therapy and in whom remissions of the disease were absent or who continued to suffer signs and symptoms even during periods of slight remission. In all patients included in this report, reliable information regarding the characteristics and severity of the clinical course was available. Some patients had been observed for years in the cardiac clinic of the Beth Israel Hospital and on the wards; others were referred by physicians who placed their records at our disposal. Each patient was appraised independently by several of us before a decision was reached; in many instances, our appraisal was based on observation and study of the patient, including exercise tolerance (29) and other tests over a period of weeks or many months before radioactive iodine therapy was instituted. Following the administration of I^{131}, the period of six to twenty-six weeks before the development of definite hypothyroidism served as an additional control period.

The patients with angina pectoris suffered characteristic attacks on effort or emotion and continued to have several or many attacks a day on slight exertion such as walking short distances, bending to tie shoe laces or walking one flight of stairs; many were awakened from sleep nightly or several times a week, and had attacks after eating; several had attacks of cardiac asthma. None of the patients had been able to carry on gainful occupation, except Nos. 7 and 22, who did light work a few hours a day and No. 11 who worked as an upholsterer for several hours a day. The severity of cardiac involvement was reflected by the fact that 23 attacks of acute myocardial infarction had occurred in the 20 patients with angina pectoris. The etiologic basis for angina pectoris in all patients was arteriosclerotic heart disease; in 7, arterial hypertension was present. Sixteen were males and 4 were females. The ages ranged from 38 to 72 years, the average being 61 years. The duration of angina pectoris prior to treatment varied from one to eighteen years and averaged 5.6 years. The duration of hypothyroidism following I^{131} therapy has been from six to twenty-two months and has averaged fourteen months (Table 1).

The 9 patients with congestive failure (Table 2) had all been treated by prolonged bed rest and regularly showed evidence of congestive failure

on getting out of bed. Six of the patients had rheumatic heart disease; 2, arterial hypertension and arteriosclerotic heart disease; and 1 patient had rheumatic heart disease and arteriosclerotic heart disease with prior myocardial infarction. The ages of the patients ranged from 41 to 59 years the average being 47 years. The duration of decompensation varied from one and a half to seventeen years and averaged six years. The condition in each case was such that definite improvement could be confidently at-

TABLE 1. SUMMARY OF RESULTS IN 20 CASES OF ANGINA PECTORIS AND ARTERIOSCLEROTIC HEART DISEASE

I. *Clinical data*		
Number of patients		20
Ages		38–72 yrs.
Sex: Male		16
Female		4
Duration of angina pectoris		1–18 yrs. (av. 5.6)
Number of prior myocardial infarctions		23
II. *I^{131} therapy*		
Dose administered		25.5–176 mc. (av. 68.3)
Number of patients with hypometabolism		17
Number of patients with insufficient period for development of hypometabolism		3
Time to onset of hypometabolism		6–26 wks. (av. 11 wks.)
Duration of hypometabolism to date		6–22 mos. (av. 14 mos.)
III. *Therapeutic results in 17 patients with hypometabolism*		
A. Worthwhile:		11
Striking	6	
Excellent	1	
Good	3	
Fair	1	
B. Not worthwhile:		6

tributed to the hypothyroidism induced by I^{131}. The duration of hypothyroidism following I^{131} therapy has been from three to twenty-two months, and has averaged sixteen months.

No patient was chosen whose prognosis for life was good. In each instance the procedure was explained to the patient with a full account of its experimental status and the necessity for frequent follow-up studies. In some patients the treatment was inaugurated while they were still hospitalized; in others, all studies were carried out with the patients on an ambulatory basis.

No patient showed positive evidence of either hyperthyroidism or hypothyroidism before treatment. In addition to the clinical criteria, the following indices revealed normal thyroid function: the basal metabolic rate, the serum cholesterol and, in some instances, the serum protein-bound

iodine. Tracer doses of I^{131} were administered and in all cases the percentage of urinary I^{131} excretion (30, 31, 32) was that observed with normal thyroid function (33). In patients with congestive failure, the urinary excretion is lower than that observed in edema-free individuals. Direct measurements of the thyroid uptake (34, 35) in patients with congestive failure have revealed higher uptakes than those observed in angina pectoris or in normal individuals (Table 3).

TABLE 2. SUMMARY OF RESULTS IN 9 CASES OF CONGESTIVE HEART FAILURE

I. *Clinical data*		
Number of patients		9
Ages		41–59 yrs.
Sex: Male		3
Female		6
Rheumatic heart disease		6
Hypertension: arteriosclerotic heart disease		2
Rheumatic and arteriosclerotic heart disease		1
Prior myocardial infarctions		3
Duration of congestive failure		1½–17 yrs. (av. 6 yrs.)
II. *I^{131} therapy*		
Dose administered		25.5–60 mc. (av. 42 mc.)
Number of patients with hypometabolism		6
Number of patients with insufficient period for development of hypometabolism		3
Time to onset of hypometabolism		7–16 wks. (av. 10 wks.)
Duration of hypometabolism to date		3–22 mos. (av. 16 mos.)
III. *Therapeutic results in 6 patients with hypometabolism*		
A. Worthwhile:		4
Striking	3	
Good	1	
B. Not worthwhile:		2

TABLE 3. THE 24-HOUR THYROID GLAND UPTAKE FOLLOWING TRACER DOSES OF I^{131} IN PATIENTS WITH CONGESTIVE FAILURE

Diagnosis	No. of patients	Average uptake of I^{131} in 24 hours %
Euthyroid, normal	32	29 (S.D. 4.8)
Hyperthyroidism	48	69 (S.D. 13.1)
Myxedema	10	8 (S.D. 3.4)
Congestive failure, euthyroid	11	35 (S.D. 8.3)

RESULTS

The effect of hypothyroidism on angina pectoris

Angina pectoris has been abolished or significantly lessened in 11 of the 17 patients with intractable cardiac pain in whom hypothyroidism or myxedema has been induced with I^{131} (Table 1). The duration of angina pectoris in these 11 patients was from one to ten years, averaging four years and six months. The improvement has been particularly striking in 7 patients (Cases 1, 2, 3, 4, 5, 19 and 22). These patients are able to undertake considerably more exertion than formerly with only occasional, or no attacks of angina pectoris. In Cases 1, 2, 5 and 22 the patients are gainfully employed, whereas prior to treatment they had been incapacitated for years because of angina which was precipitated by the slightest effort. In the other 4 of the 11 patients, the result has been definitely worthwhile according to the appraisal by the patient and by us. In addition to the foregoing 11 patients, 1 patient (Case 14), incapacitated primarily because of congestive failure, also suffered angina pectoris on moderate exertion. With improvement in the congestive failure, angina pectoris no longer occurs.

In the remaining 6 of the 17 patients with angina pectoris, the therapeutic result has not been striking. In Cases 8 and 9, angina pectoris was relieved for six and nine months respectively but has since relapsed to pretreatment status. In the 4 patients (Cases 10, 11, 12 and 13) in whom the therapeutic result was not considered worthwhile, angina pectoris was definitely lessened when the patients exhibited the clinical and laboratory evidences of myxedema. It was impossible, however, to maintain these patients at such metabolic levels because of the discomfort of myxedema. When desiccated thyroid was administered in order to ameliorate the discomfort of myxedema, attacks of angina pectoris occurred with sufficient frequency and severity to make us consider the result not worthwhile.

The effect of hypothyroidism on congestive heart failure, paroxysmal nocturnal dyspnea and pulmonary edema

Nine of the 29 patients were incapacitated primarily because of congestive heart failure (Table 2). Four of the 6 patients in whom hypothyroidism has been induced for from three to twenty-two months have showed worthwhile improvement; in 3, the improvement has been striking. The relief from dyspnea, attacks of pulmonary edema and paroxysmal nocturnal dyspnea has been associated with objective evidences of diminution or disappearance of perpiheral edema and of pulmonary congestion. In patient No. 15, orthopnea and ascites have disappeared, the liver is no longer palpable, cyanosis has disappeared and the vital capacity of the

lungs has increased from 2,200 cc. to 3,650 cc. The patient is able to engage in useful activity for the first time in one and a half years.

In the 2 patients in whom a worthwhile therapeutic effect could not be ascribed to I^{131} therapy, definite improvement of congestive failure occurred in 1 (No. 17) but this may have been due to improvement in the concomitant rheumatoid arthritis. In the other patient (No. 18) definite temporary improvement was evident for approximately one month, followed by relapse to her pretreatment status.

In addition to these 6 patients, symptoms and signs of congestive failure were present in many of those incapacitated primarily because of angina pectoris. Congestive failure had been noted for ten years in Case 4 and for five years in Case 6 with episodes of peripheral edema, pulmonary congestion, recurrent paroxysmal nocturnal dyspnea and orthopnea. Paroxysmal dyspnea and attacks of acute pulmonary edema had also occurred in Cases 2 and 3. In all of these patients the significant improvement in angina pectoris was associated with comparable improvement in the manifestations of congestive failure, the signs and symptoms being impressively relieved or entirely dissipated.

Induction of myxedema with I^{131}. Measurement of the thyroid radiation

Recent studies have permitted estimation of the radiation necessary to induce myxedema by means of I^{131} in euthyroid patients with normal thyroid glands. Measurement of the thyroid gland uptake was made by the method previously described (32, 34). The effective (36) or biologic (37) half-life was measured similarly. The calculation of equivalent roentgens (38) of thyroid radiation was made by the following formula (37):

$$\text{Equivalent roentgens (I)} = \frac{\text{microcuries administered} \times \%\ \text{uptake}}{\text{grams thyroid weight (II)}} \times \frac{\text{effective half-life (III)}}{8} \times 160\ \text{(IV)}$$

(I) One roentgen-equivalent-physical (R.E.P.) is defined as an amount of radiation (other than protons) which releases in tissue an amount of energy equal to the energy loss of one roentgen of gamma radiation absorbed in air.

(II) The normal thyroid gland has been estimated to weigh 30 grams. This may be regarded by some as too high by approximately 5–10 grams.

(III) Effective or biologic half-life of the isotope in tissue includes the rate of elimination from the tissue and the physical rate of disintegration of I^{131}.

(IV) The number of equivalent roentgens delivered in one gram of tissue

TABLE 4. THE DOSE, 24-HOUR THYROID GLAND UPTAKE AND ESTIMATED THYROID RADIATION IN 8 EUTHYROID PATIENTS WITH CONGESTIVE FAILURE OR ANGINA PECTORIS, GIVEN THERAPEUTIC DOSES OF I^{131}

Case No.	Diagnosis	Date of treatment	I^{131} dose, millicuries	24-Hour thyroid gland uptake, %	72-Hour urinary excretion, %	Biologic half-life, days	Estimated thyroid gland weight, Gm.	Estimated thyroid radiation, R.E.P.	Comment
22	Angina pectoris	6/7/49 6/15/49	26.5 22	36.8 8.1	64 97	6.4 1.9	30 30	41,400 2,300 43,700	Hypometabolism (9 wks. after treatment)
23	Angina pectoris	1/3/50 1/11/50 1/23/50	20.5 25 27.5	26.2 12.9 7.8	76.5 74.5 75.1(1)	4.2 — 2.2	35 30 25	14,000 4,100	No hypometabolism (6 wks. after treatment) (1) 48-hr. collection
24	Angina pectoris	10/10/49 10/17/49	20 11.5	24 13.3	63 73.5	8 —	30 30	25,400 8,100 33,500	No hypometabolism (15 wks. after treatment)
25	Angina pectoris	1/16/50 1/24/50	25 25	49 6.9	42 —	6.6 1.5	30 30	54,400 1,700 56,100	No hypometabolism (5 wks. after treatment)
26	Rheum. ht. dis. Cong. ht. failure	9/9/49 9/16/49 9/26/49	20 15.5 25	32.2 7.8 1.6	67 83 76.5	6.6 1.1 .8	30 30 30	28,400 880 220 29,500	Hypometabolism (10 wks. after treatment)
27	Rheum. ht. dis. Cong. ht. failure Angina pectoris	10/24/49 11/3/49	24.5 20	27 3.6	59.5 82.5	6.4 1.7	30 30	28,000 800 28,800	Early hypometabolism (14 wks. after treatment)
28	Rheum. ht. dis. Cong. ht. failure Angina pectoris	11/3/49 11/11/49	20 20	36.3 10	16.5 24	6.7 2.1	30 30	32,500 2,800 35,300	No hypometabolism (13 wks. after treatment)
29	Rheum. ht. dis. Cong. ht. failure	2/8/50 2/16/50	30.5 23	42.3 7.4	— —	5.7 .8	30 30	49,000 900 49,900	

during the total decay of one microcurie of I^{131} (39); 144 due to the interaction of beta rays with tissue and 16 due to gamma rays.

In 8 patients (Table 4) the equivalent roentgens delivered to the thyroid gland by 31.5 to 73 millicuries of I^{131} has ranged from 28,800 to 56,100. In 3 patients (Cases 22, 26 and 27) hypothyroidism or myxedema has been induced by 28,800 to 43,700 R.E.P. in from nine to fourteen weeks. It is of interest that similar measurements made in our laboratories show that the effective therapeutic level in patients with hyperthyroidism is approximately 12,000 R.E.P. (40). In euthyroid cardiac patients given multiple doses at approximately one-week intervals the vast majority of the radiation is delivered by the initial dose (Table 4; Fig. 1).

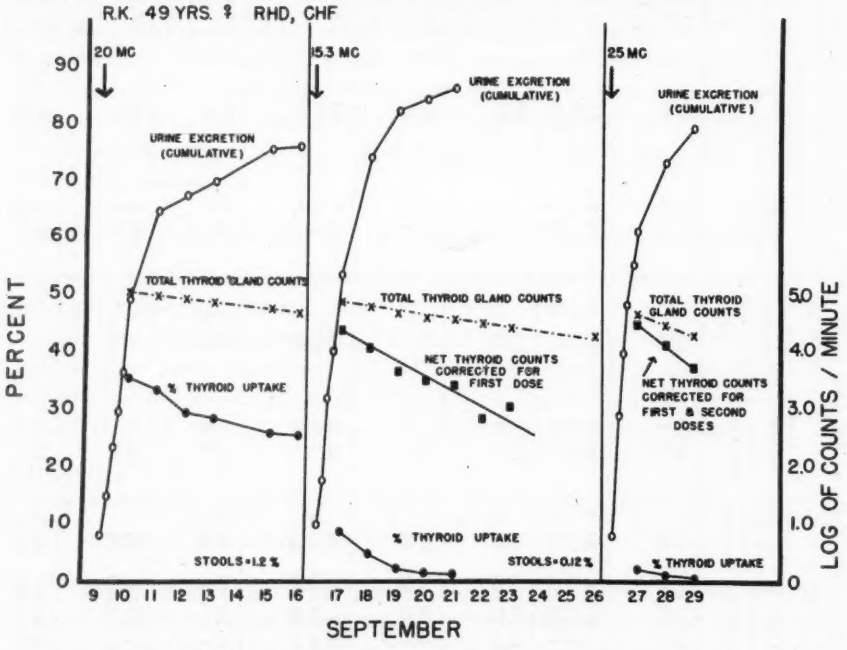

FIG. 1. The thyroid gland uptake, turnover, cumulative urine excretion and the stool excretion of I^{131} following the oral administration of 20, 15.3 and 25 millicuries of carrier-free I^{131} in Case 26 (*see* Table 4 for radiation delivered by each dose). The thyroid uptakes following the second and third doses are strikingly less than following the first dose; the turnover (biologic half-life) is faster and the urinary excretion is greater.

SUMMARY AND CONCLUSIONS

1. The therapeutic results of hypothyroidism induced by radioactive iodine (I^{131}) in 23 euthyroid patients with intractable advanced angina pectoris or congestive failure are reported. The duration of observation

after induction of hypothyroidism varied from three to twenty-two months and averaged fifteen and a half months. In 6 additional patients treated with therapeutic doses, the period of observation has been too short for evaluation; hypothyroidism has not yet developed.

2. Persistent hypothyroidism can be regularly induced by one or more appropriate doses of radioactive iodine.

3. No radiation sickness and no toxic effects on the blood or kidneys have been observed. There was no thyroiditis in 10 patients; mild or moderate transitory thyroiditis in 18; and severe thyroiditis in only 1. Temporary mild hyperthyroidism occurred in 2 patients.

4. Each patient received orally a total of from 25.5 to 176 millicuries of I^{131} in single or divided doses. The largest single dose was 56 millicuries.

5. The average total dose was 61 millicuries. In 8 patients recently studied the radiation delivered to the thyroid gland has been 28,800 to 56,100 R.E.P. In 3 patients hypothyroidism has been induced in from nine to fourteen weeks with 28,800 to 43,700 R.E.P.

6. Angina pectoris has been strikingly lessened or abolished in 11 of the 17 patients with intractable cardiac pain. Several patients have been rehabilitated and are gainfully employed. Concomitant congestive failure, present in several of these patients, was likewise improved. In the other 6 of the 17 patients, angina pectoris was relieved when the patients were myxedematous but recurred when desiccated thyroid was administered in order to ameliorate the discomfort of myxedema.

7. Four of 6 patients, incapacitated primarily because of congestive heart failure, have shown worthwhile improvement; in 3 of these the improvement has been striking.

8. In the clinical management of these patients, we have attempted to maintain the lowest metabolic rate consistent with the comfort of the patient and have administered small doses of desiccated thyroid after the induction of myxedema.

9. Final evaluation of this therapy must await prolonged study. At present it can be said that many months of worthwhile existence already have been added to the lives of these disabled cardiac patients who were refractory to all standard forms of medical therapy.

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EFFECTS OF ADRENAL AND GONADAL PRODUCTS ON THE WEIGHT AND RADIOIODINE UPTAKE OF THE THYROID GLAND IN THE RAT*†

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INTRODUCTION

NUMEROUS reports suggest that the adrenal glands may be involved in the maintenance of normal thyroid function. Unfortunately, much of the information available is based on clinical impression, or sketchy and brief animal studies. It has been suggested by several investigators that the adrenals are involved in the thyrotoxicosis of Graves' disease. Marine (1) postulates adrenal hypofunction in hyperthyroidism, whereas Crile (2) feels the adrenal glands are hyperactive in the same disease. The fact remains as Means (3) states "Nothing definite is known about the role of the adrenals in human thyrotoxicosis."

On the other hand, there is a certain amount of contradictory information available regarding the possible relationship of the gonads to thyroid physiology. Clinical and experimental evidence would indicate that some interrelationship exists between the gonads and the thyroid gland. The exact relationship is, however, obscure.

Many investigators have reported changes in the thyroid following castration. This operative procedure has been reported by Anderson and Kennedy (4) and others, to produce a decrease in follicular epithelium and cause an increase in colloid storage within two months after castration. Chouke (5), and Starr and Bruner (6) were, however, unable to find

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these changes within one month following castration. Using different species of animals, other investigators have reported that hyperplasia of the thyroid follows gonadectomy.

The administration of testosterone propionate to the immature female rat has been reported by Nathanson, Brues and Rawson (7) to result in a stimulation of both the thyroid and parathyroid glands. This effect was manifest by increased mitotic activity and an increase in acinar cell height. These investigators suggested the mechanism of this reaction to be via the anterior pituitary gland. In a recent report before this society, Gassner, Barrett and Gustavson (8) showed that testosterone propionate given over an extended period of time to the intact male rat produces a decrease in thyroid iodine. This treatment also produced a decrease in response to a goitrogenic diet but not to the same degree as observed in estrone-treated females. This suggested a possible difference in the mechanism responsible for thyroid depression in the two sexes.

Estrogenic substances have been variously reported to inhibit or stimulate the thyroid by many investigators. Freudenberger and Clausen (9) postulated that theelin (estrone) injections stimulate the anterior pituitary to liberate increased amounts of thyroid-stimulating hormone. In addition to this mechanism, Grumbrecht and Loeser (10) concluded that in the castrated female rat the uterus is involved in restoration of the thyroid to normal by estrogen treatment. These authors found that intra-uterine estrogen was essential to produce restoration of the thyroid once castration changes were established. Alexiu (11), however, observed that a combination of castration and estradiol benzoate produced a greater degree of hyperplasia than either treatment alone. Emge and Laqueur (12) and Schilling and Laqueur (13) using "thyrohyperplastic" rats, concluded that neither castration nor estrogenic treatment influenced the hyperplastic glands. In rabbits treated with estrogen Chu and You (14) found the thyroid stimulated to a hyperfunctional state which suppressed the follicle-stimulating hormone activity of the pituitary but stimulated the luteinizing hormone activity.

It is quite probable that the effects of estrogen on thyroid activity depend to a large extent on dosage. Large doses or prolonged treatment definitely depress the thyroid and basal metabolic rate. Small doses for short periods of time tend to increase the basal metabolic rate and thyroid weight. Pincus and Werthessen (15), Sherwood and Bowers (16), Gassner, Barrett and Gustavson (8), Koenig, Gassner and Gustavson (17) and others have shown quite conclusively that estrone and diethylstilbestrol significantly decrease the thyroid iodine of the rat.

Little is known regarding the effect of progesterone on thyroid activity. For example Grumbrecht and Loeser (10) found the luteal hormone to have

no influence on the thyroid. Alexiu (11), on the other hand, observed epithelial proliferation following administration of progesterone. Emge and Laqueur (12) noted that progesterone decreases the goitrous changes caused by wheat germ in the diet they were using.

The relation of the adrenal gland to normal thyroid function has apparently not been too well investigated. However, certain clinical and experimental studies suggest a possible relationship between the two endocrine organs. For example, Stewart and Rogoff (18) observed that glycerol extracts of ox adrenal cortex when fed to patients with Graves' disease caused a gain in weight, muscle improvement and a decrease in basal metabolic rate. Szent-Györgi (19) reported the isolation from the adrenal cortex of a substance which, upon administration to animals, produced thyroid involution.

It has been reported that in several species of laboratory animals injuries to the adrenal cortex, or infections result in hyperplasia of the thyroid (Mahorner (20)) as well as increased heat production. Since an increased metabolic rate does not occur in thyroidectomized animals treated in a similar fashion it has been postulated that the adrenal cortex produces some substance which acts on the thyroid. Others have suggested that the hyperpyrexia which results from adrenal injuries can be explained on the basis of absorption of toxic products from the degenerating glands or from infections which would increase the basal metabolic rate. Soffer and associates (21) studied the role of the adrenal in thyroid function following parenteral injection of epinephrine. These authors observed that in both the intact and thyroidectomized dog, administration of epinephrine resulted in an increased secretion of thyroid-stimulating hormone. Treatment of the rat with epinephrine has been found to decrease the uptake of I^{131}. This is in contrast to adrenalectomized animals, in which epinephrine increases the collection of iodine (Soffer, Gabrilove and Jailer (22)). These latter investigators reported that the simultaneous administration of epinephrine and cortisone in adrenalectomized animals produced a marked reduction in the uptake of radioactive iodine.

In view of the discrepancies discussed above, it was felt desirable to investigate further the possible role the adrenal and gonads play in normal thyroid physiology. We, therefore, set up a technique for screening compounds in an attempt to evaluate their relative effects on the thyroid. The criteria used were: 1) thyroid weight changes, 2) uptake of radioactive iodine by the thyroid, 3) thyroid epithelial height change, 4) pituitary weight change, and 5) the pituitary content of thyroid-stimulating hormone. This report deals only with the change in thyroid weight and the collection of radioactive iodine by the thyroid.

MATERIALS AND METHODS

The animals used in this study were male rats of the Sprague-Dawley strain with a weight which varied between 250 and 300 grams. Each group consisted of approximately 10 animals. After the animals were selected for uniformity of weight and health they were maintained on a low iodine diet[1] and double distilled water for the duration of the experiment. Ten

TABLE 1

Compound	Source	Solvent	Total dose/ animal
17α-Hydroxy-11-desoxycorticosterone -21-acetate (compound S acetate)	Glidden Company	H_2O suspension	50 mg.
Δ^4 Pregnene 17α, 20β, 21-triol-3-one 20, 21, -diacetate ("Triol")	Glidden Company	H_2O suspension	50 mg.
Allo-pregnanediol-3β, 17α-one-20-acetate (compound L acetate)	Chemical Specialties Company	Suspension	150 mg.
Adrenal cortex extract	Upjohn Company	H_2O extract	21 cc.
Pregnenolone	Schering Corp.	Suspension	150 mg.
21-Acetoxy-pregnenolone	Schering Corp. and Syntex Company	Suspension	150 mg.
Adrenalin chloride	Parke, Davis & Co.	Saline (1,1000)	2.0 cc.
Progesterone (Proluton)	Schering Corp.	Oil	50 mg.
Testosterone propionate (Oreton)	Schering Corp.	Oil	50 mg.
Estrone (Theelin)	Parke, Davis & Co.	Oil	500 γ
Estradiol benzoate (Progynon-B)	Schering Corp.	Oil	10 mg.
Cortisone acetate	Merck & Co.	Suspension	25 mg. 50 mg.
ACTH	Armour Laboratories	Saline	50 mg. (Armour standard)
Desoxycorticosterone acetate (Cortate)	Schering Corp.	Oil	10 mg.

days after the special diet was started, injection of the various compounds to be tested was begun. With the exception of compounds in oil, all injections were given three times a day, approximately every eight hours. Treatment with the various compounds was continued for ten days.

Twenty-four hours before autopsy all animals were given 1 microcurie of carrier-free I^{131} intraperitoneally. At the time of autopsy the animals were given a small dose of Nembutal and exsanguinated.

[1] NaCl—50 Gm.; Brewers' yeast—10 Gm.; calcium carbonate—150 Gm.; corn—3,800 Gm.; wheat gluten—100 Gm.

Tissues were removed, dissected free of fat and connective tissue and weighed on a Roller-Smith balance. They were then immediately put into a 10 cc. vial containing 4 cc. of a solution of 3 parts Bouin's solution and 1 part 1 per cent NaI. (The NaI was added to minimize the volatilization of the I^{131} from the acid Bouin's solution.)

A Texas Company gamma-ray Geiger-Müller tube, designed so that multiple center wires are arranged vertically around a center well, was

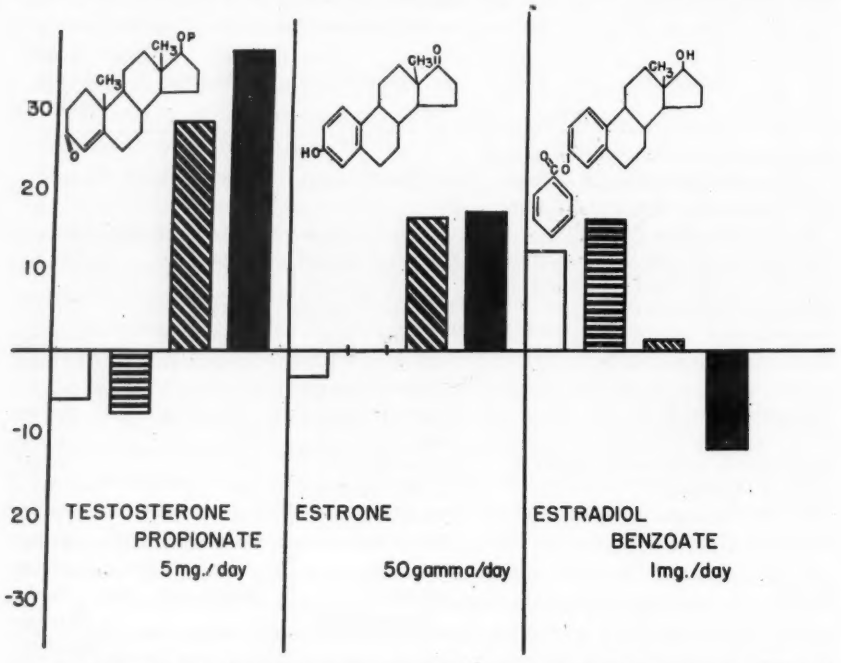

FIG. 1. Both testosterone propionate and estrone significantly increase iodine collection. Estradiol benzoate does not. Thyroid-body ratio is increased with estradiol due to decrease in body weight and slight increase in thyroid weight. (Open blocks in all figures are thyroid weights. Cross-lined blocks are thyroid-body ratio. Diagonal-lined blocks represent per cent I^{131}/gland. Solid blocks are per cent I^{131}/thyroid-body ratio. Figures show relative per cent increase or decrease with respect to control value.)

used for all I^{131} determinations. In effect, the sample was surrounded by the counter. All samples were placed in identical tubes containing the same amount of fluid and placed in the same position within the tube. This arrangement of source and counter resulted in accurate activity determinations when there was as little as 0.01 microcurie of I^{131} per vial.

The I^{131} in the samples has been expressed as a percentage of the original

I^{131} injected, based on a dilution of the original solution, measured at the same time and under the same conditions as the sample.

The compounds we have tested, their source and the total dosage per animal are given in Table 1.

EXPERIMENTAL RESULTS

For comparative purposes we have considered the control determinations in each series of compounds tested to be 100 per cent. Experimental

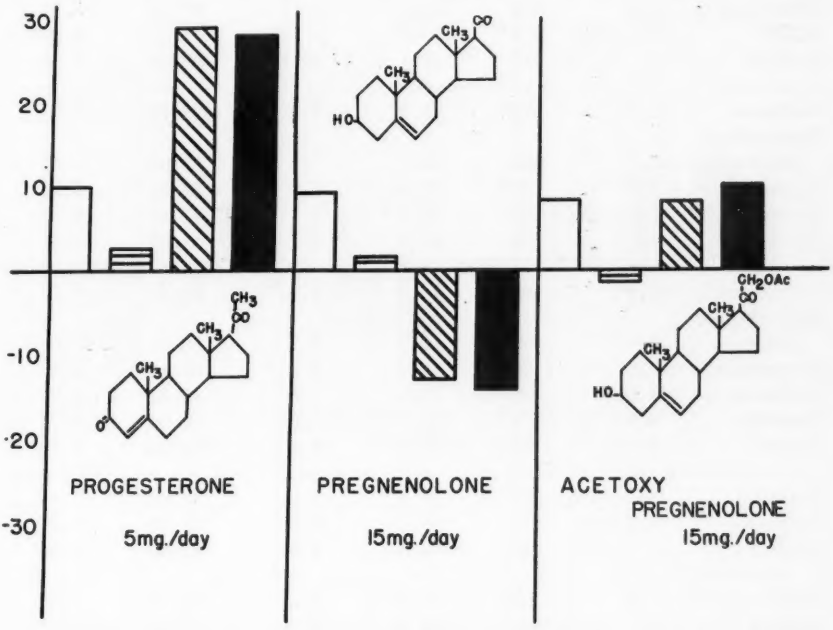

FIG. 2. Progesterone increases iodine collection by the thyroid, whereas the other two compounds do not. There is a suggestion that pregnenolone decreases iodine uptake. This is not, however, statistically significant.

groups are then reported as a relative per cent increase or decrease with respect to the control value. The results obtained using this method are shown graphically in Figures 1 to 5.

The actual results obtained when animals were treated with the various substances are shown in Table 2. These results concern body weight, thyroid weight, the thyroid weight per 100 grams of body weight, per cent uptake of I^{131} per thyroid gland, and the per cent of I^{131} per mg. of thyroid

TABLE 2

Compound	Mg./day/ rat	Average body wt. (Gm.)	Average thyroid wt. (mg.)	$\frac{\text{Thyroid}}{\text{Body}} \times 100$	Per cent I^{131}/ thyroid	Per cent I^{131} $\frac{\text{Thyroid}}{\text{Body}} \times 100$
"Triol"	5.0	266	23.3	8.75	55.60	6.37
Adrenal cortex extract	2.1 (cc.)	261	23.5	9.00	56.60	6.37
Compound S	5.0	269	24.6	9.17	53.50	5.84
ACTH	5.0 (std.)	228*	19.9*	8.75*	44.50*	5.09*
Control	—	269	27.1	10.1	58.90	5.94
Cortisone	2.5	238*	18.6*	7.8	38.75	5.0
Testosterone propionate	5.0	283	20.3	7.1	52.65*	7.4*
Progesterone	5.0	293*	23.5	7.9	53.30*	6.9*
Estrone	50 (gamma)	268	20.7	7.7	47.80*	6.3*
Control	—	278	21.4	7.7	41.06	5.4
Compound L	15.0	284*	19.0	6.7	68.50	10.2
Acetoxy-pregnenolone	15.0	290*	19.5	6.7	66.30	10.0
Pregnenolone	15.0	283*	19.6	6.9	53.40	7.8
Cortisone	5.0	230*	17.6	7.7*	45.50*	5.9*
Estradiol	1.0	256*	20.1	7.9*	62.00	8.0
Control	—	267	18.0	6.8	61.30	9.1
Formalin	1 cc. (4%)	304	17.8	5.5	40.40	7.4
Adrenalin	0.2 (cc.)	292	20.5	6.9	36.10	5.2*
Control	—	298	19.6	6.5	41.80	6.4
DCA	1.0	337*	21.8*	6.5	28.90	4.4*
Control	—	297	19.3	6.5	30.80	4.7

* Indicates probable significant difference from the control values.

per 100 grams of body weight. These results represent the average of each group of animals studied.

I. The effects of gonadal substances

1. *Testosterone propionate.* In the dosage tested, testosterone propionate produced no significant change in body weight, thyroid weight, or thyroid-body weight ratio. However, there was a significant increase in the uptake of radioactive iodine by the thyroid gland. This can be seen by examination of Table 2 and Figure 1.

2. *Estrone.* In a dosage of 50 gamma per day, estrone produced no effect on the weights. A significant rise in the uptake of iodine, however, was observed.

3. *Estradiol benzoate.* One milligram of estradiol benzoate did not influence significantly the thyroid weight or the uptake of I^{131}. There was, however, a suggestion of a significant increase in the thyroid-body weight ratio, which reflected a decrease in body weight.

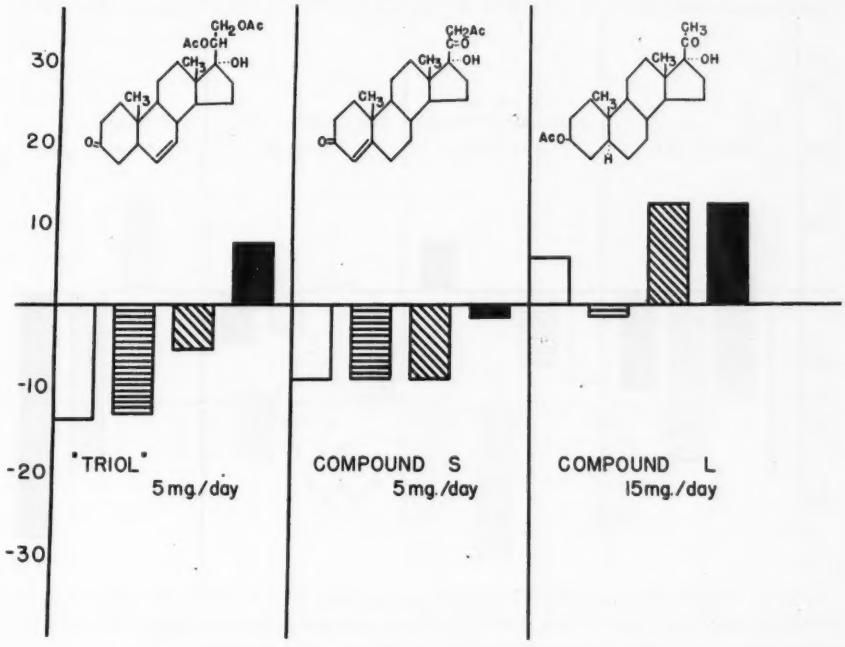

FIG. 3. The compounds above show no appreciable deviation from control values.

4. *Progesterone.* Progesterone did not appreciably increase the thyroid weight although the average body weight was slightly increased. It did raise the percentage of radioactive iodine collected by the thyroid gland.

5. *Pregnenolone.* In a dose three times that of progesterone, this compound did not increase the thyroid weight, although the body weight was increased. There is a suggestion that pregnenolone decreases the uptake of I^{131}.

6. *Acetoxy-pregnenolone.* In a dose equivalent to that used with pregnenolone this steroid produced an increase in body weight but no change in thyroid weight or iodine uptake.

II. The effects of adrenal substances

1. *Adrenal cortex extract.* Using 2.1 cc. per day (105 dog units) of Upjohn's saline extract, we found no significant change in weights or iodine uptake.

2. *"Triol"* (Δ^4 *pregnene 17α, 20β, 20-triol-3-one-20, 21-diacetate*). In the dose we used, this agent did not show any appreciable effect.

3. *Compound S* (*17α-hydroxy-11-desoxy-corticosterone-21-acetate*). Com-

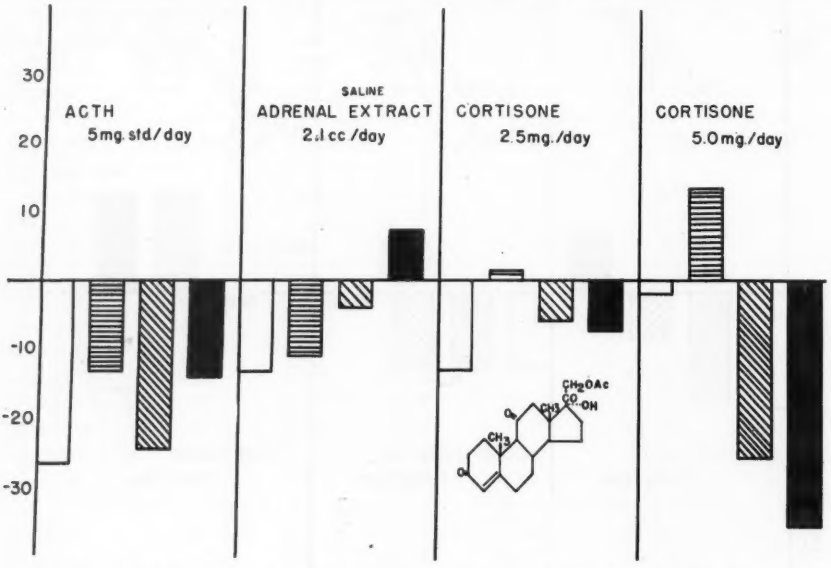

FIG. 4. ACTH depresses thyroid weight and uptake of I^{131}. Adrenal extract has no statistical effect. Cortisone in a dose of 2.5 mg. decreases thyroid weight but not with higher doses. A dose of 5.0 mg. definitely depresses iodine collection.

pound S did not produce any change in thyroid weight or iodine concentration.

4. *Compound L* (*allo-pregnanediol-3β, 17α-one-20-acetate*). This compound produced an increase in body weight but no other significant deviation from the control animals.

5. *Desoxycorticosterone acetate.* DCA increased the body weight and thyroid weight over control values. However, the thyroid-body weight ratio was not changed. There is a suggestion that the iodine uptake is depressed with this compound.

6. *Cortisone.* We have tested cortisone in doses of 2.5 mg. and 5.0 mg. In both cases the animals lost essentially the same amount of body weight.

With 2.5 mg. the loss in thyroid weight was greater than with the higher dose. This makes it appear that cortisone significantly decreases the thyroid weight. However, since the higher dose did not decrease the weight of the thyroid gland it is difficult to evaluate these results. The thyroid-body weight ratio appears to be depressed with the higher dosage of cortisone. Iodine uptake is decreased significantly only with the dose of 5.0 mg.

7. *Adrenalin chloride.* In the dose we have used, there was a suggestion that iodine collection by the thyroid is depressed by administration of adrenalin.

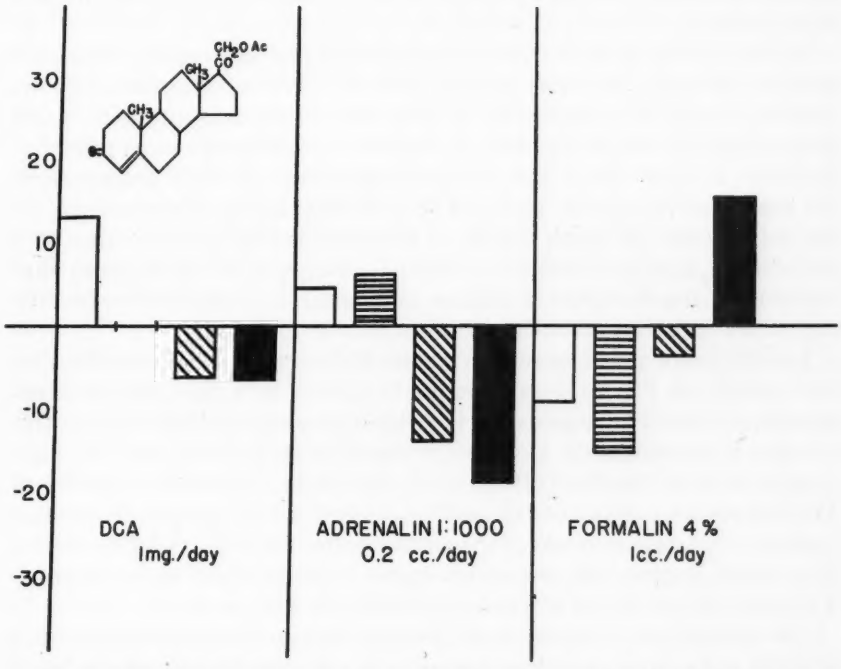

FIG. 5. Both thyroid weight and body weight are increased with DCA. There is a suggestion that the I^{131} thyroid-body ratio is depressed. Adrenalin decreases the uptake of iodine in the normal animal. Formalin has no significant effect in this series.

III. Other substances tested

1. *Adrenocorticotropin.* ACTH produced a marked decrease in body weight, thyroid weight and uptake of radioactive iodine.

2. *Formalin.* We have tested formalin as a nonspecific control and found, with the dose used, no effect on either weight or iodine uptake.

DISCUSSION

As was indicated in the introduction to this paper, it is possible that some relationship exists between the adrenal, or the gonads, and normal thyroid function. We have tested substances from both the adrenal gland and the gonads and determined their effect on normal thyroid function as evidenced by changes in weight and uptake of radioactive iodine. It is quite obvious that we have been unable to assay all the adrenal cortical steroids which have been isolated. Consequently it is impossible, at this time, to conclude definitely the exact role adrenal products play in thyroid regulation. Nevertheless, some information has been obtained which merits further consideration.

Of the steroids we have tested, 3 out of 6 gonadal substances produced a definite difference in iodine uptake, without influencing appreciably the thyroid weight. It is interesting to note that testosterone propionate and progesterone in equivalent doses produced essentially the same response. However, in a dose three times that of progesterone, acetoxy-pregnenolone did not affect the uptake of I^{131} to a significant degree. Pregnenolone, on the other hand, although failing to alter the iodine concentration to a statistically significant extent, produced a response which suggests that iodine uptake is decreased in relation to the control value. Further investigation of this compound seems necessary.

It is interesting that estrone in a dose of 50 gamma increased the thyroid uptake of I^{131}, whereas estradiol benzoate, in a dose twenty times greater, produced no response. It is possible, as suggested earlier, that this is a dose response picture. However, it should be pointed out that Paschkis, Cantarow, and Peacock (23) found no significant difference in uptake of I^{131} between normal intact rats and those receiving 50 gamma of estradiol benzoate three times weekly for one, three and one half, and four weeks. This might suggest that not all estrogenic substances act on the thyroid. Further study of related compounds is definitely necessary.

The mechanism of action of the gonadal substances on the thyroid is a difficult and complex problem. Gassner, Barrett, and Gustavson (8) found that with both estrone and testosterone given over extended periods of time, thyroid depression was produced. They postulated that these substances produce a deficiency of the thyroid-stimulating hormone. If this theory is correct, our results must be interpreted to indicate that the steroid treatment first stimulates the gland directly or indirectly to take up increased iodine. Prolonged treatment then produces a reversal of this response and the gland concentrates less iodine, as observed by Gassner, Barrett and Gustavson. Another possible explanation is that short-term treatment with these substances directly stimulates the thyroid to collect

iodine. Later reversal is due to stimulation of the adrenal which produces some substance depressing to the thyroid gland.

The studies which we have done on adrenal substances in relation to thyroid physiology do not clarify appreciably any relationship which might exist between the two glands. This work tends to confirm the action of epinephrine on uptake of I^{131}, as reported by Soffer, Gabrilove and Jailer (22). Although our reported results with this drug are not mathematically significant, we have unpublished data which show that epinephrine does depress iodine uptake in the normal rat. Conversely, in the adrenalectomized animal epinephrine reverses this effect. Soffer and co-workers found that cortisone inhibits the thyrotropin-stimulating effect of epinephrine. This would suggest that possibly epinephrine acts in the normal animal to increase cortisone liberation, which then overrides the adrenalin response and results in a decreased uptake of I^{131}. In the absence of the adrenal, cortisone (or some other substance) is not released and epinephrine raises the uptake of I^{131} in the thyroid gland.

Our studies show that both ACTH and cortisone in the doses used decrease the ability of the rat thyroid to collect iodine. Whether this indicates that the ACTH response is due to a secretion of only cortisone is impossible to answer at the present time. ACTH could be causing the release of other substances which might produce a decrease in iodine collection. Clarification of this question will depend on the testing of many other adrenal steroids.

In order to eliminate the possibility of the compounds tested reproducing a portion of the "alarm reaction," a group of animals were given a nonspecific substance. Treatment with formalin in the same way we gave other compounds showed no obvious effect on the thyroid or body weights or collection of I^{131}. This is in contrast to a recent report by Paschkis, Cantarow, Eberhard and Boyle (24) which reports that formalin decreases I^{131} uptake. Since we observed no effect from this agent, we feel that any response obtained with the various compounds tested is probably valid. The exact mechanism of action and the response of other steroids remains for future investigation.

SUMMARY

1. A procedure for testing adrenal and gonadal substances on the weight and uptake of radioactive iodine of the thyroid is presented.

2. Testosterone propionate and progesterone in the dosage used were found to increase the collection of radioactive iodine.

3. The results suggest that pregnenolone inhibits the ability of the rat thyroid to collect iodine.

4. Estrone was found to increase the collection of iodine, whereas a dose

of estradiol benzoate twenty times greater did not influence I^{131} uptake.

5. Both ACTH and cortisone significantly decrease the uptake of radioactive iodine.

6. It is suggested that epinephrine decreases the uptake of I^{131} in the normal animal.

7. Since formalin did not appreciably influence iodine collection, it is assumed the compounds were probably not working as an alarming stimulus.

8. Further studies using these and other compounds are deemed necessary.

Acknowledgment

We wish to express appreciation to Dr. Konrad Dobriner and to Dr. Wendell Peacock for their interest and assistance in these studies.

We should also like to thank Dr. Edward Henderson, Schering Corporation; Dr. Percy Julian, Glidden Company; Dr. John R. Mote, Armour Laboratories; Dr. Randolph Major, Merck & Company; and Dr. Irving Sollins, Syntex Company, whose collaboration in supplying the compounds made this study possible.

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CANCER OF THE THYROID IN CHILDREN: A REPORT OF 28 CASES*†

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THE following report is an analysis of 28 cancers of the thyroid seen in children between the ages of 4 and 18 years at the Memorial Hospital. They constitute 6.5 per cent of the 430 cancers of the thyroid seen at Memorial Hospital during the sixteen-year period between 1932 and 1948.

The purposes of this report are threefold:

1. To discuss the histologic types and metastasizing properties of cancers of the thyroid in the children that we have studied.
2. To discuss possible etiologic factors as suggested from an analysis of environmental, familial, and other biologic factors recorded in the histories of these patients.
3. To emphasize the importance of considering cancer of the thyroid in the differential diagnosis of tumors of the neck in children.

HISTOLOGIC TYPES

The 28 cases are catalogued according to the classification of thyroid carcinoma used at Memorial Hospital. This is a relatively simple classifi-

THYROID CANCER IN CHILDREN

HISTOLOGIC TYPES	NO. OF CASES	PER CENT
Papillary	15	54
Alveolar and Follicular	8	29
Solid	4	14
Unclassified	1	3

FIG. 1. Histologic types.

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cation which can be correlated with the clinical prognosis and the radio-iodine-concentrating function of the tumors as demonstrated by radio-autographic studies.

Our cases fall into the following groups (Fig. 1):

Papillary carcinoma comprises 46 per cent of all thyroid cancer reported from this hospital (1). It is characterized microscopically by the presence

FIG. 2. Papillary carcinoma of the thyroid. Radioautograph showing no evidence of I^{131} pick-up. ×400.

of small stalks of connective tissue covered with cells resembling thyroid epithelium. Acini with or without colloid occur not infrequently and often make up considerable portions of the neoplasm. In 7 of our cases there were tumors in which a papillary structure made up more than 85 per cent of all specimens examined. In the remaining 8 cases, although the tumors were predominantly papillary, they also showed admixtures of alveolar, follicular, or solid components. Figure 2 illustrates the histologic structure and negative iodine-concentrating capacity of a papillary carcinoma of the

thyroid as revealed by one radioautographic method of study.

Alveolar and follicular carcinoma comprises 7 per cent of the cases of thyroid carcinoma seen at Memorial Hospital. Microscopically, alveolar and follicular carcinoma shows the formation of glandular spaces devoid of colloid as far as can be judged in histologic sections (alveolar type), and

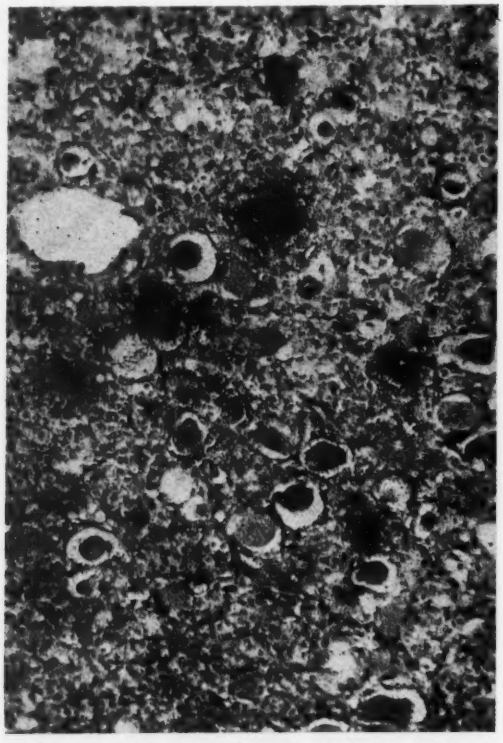

FIG. 3. Alveolar and follicular carcinoma of the thyroid. Radioautograph demonstrating varying concentration in the colloid of the follicles. ×200.

the presence of *follicles* with colloid (follicular component). Two cases presented the histologic picture of "metastasizing struma," which we believe to be a well differentiated follicular carcinoma. Two other cases showed additional histologic features to a minor degree, of solid or papillary forms. Figure 3 illustrates the histologic structure and iodine-concentrating capacity by the colloid of an alveolar and follicular adenocarcinoma.

Solid carcinoma makes up 19 per cent of the thyroid carcinomas reported from this hospital. Microscopically, solid carcinoma is characterized by cords, groups, or nests of cells growing without evidence of follicles, papillae

or significant alveolar formation. The cells are relatively uniform in regard to the size and shape of the nucleus. Figure 4 illustrates the histologic structure of a solid carcinoma of the thyroid. Three operative specimens revealed the presence of a relatively pure solid type throughout all tissues

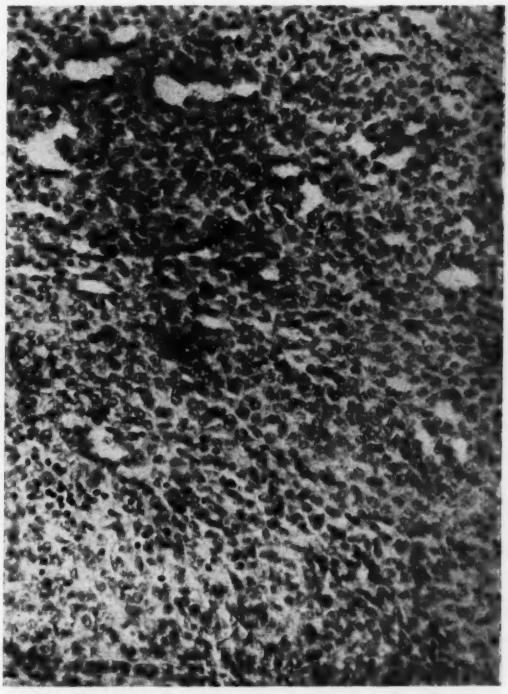

FIG. 4. Solid carcinoma of the thyroid. ×400.

containing tumor. Specimens from Case 15 contained some alveoli, follicles, and papillae but in minor amounts.

There was one particularly unusual tumor in this series. The lesion was a well encapsulated, "adenoma," 2 cm. in diameter, in the right lobe of a 13-year-old female (Case 13). A histologic section (Fig. 5) showed the tumor to be composed principally of spindle cells which had a plexiform arrangement. There were occasional areas which resembled Hürthle cells, as indicated by a large amount of acidophilic cytoplasm. Although debatable as to histologic type, it was felt after study of multiple sections that this lesion most likely represented a variant of Hürthle cell carcinoma. It is listed as *unclassified.*

Significance of histologic classification

Much has been said and written about the variability of the histologic pattern of thyroid carcinoma. Seventeen of our cases showed a uniform histologic pattern making up about 85 per cent of the primary and meta-

FIG. 5. Unclassified carcinoma of the thyroid (Case 13). The cells in the center of the section showed large amounts of acidophilic cytoplasm with hematoxylin-eosin stain. ×400.

static lesions when all materials were considered. On the other hand, it should be pointed out that there are mixed tumors. One patient, the youngest in our series, had an admixture of papillary, solid, follicular, and alveolar components in all specimens examined. In another, the primary tumor was predominantly papillary with a small follicular component, whereas a cervical metastasis showed the reverse. Classification on the basis of a single biopsy specimen is obviously hazardous.

Because of the relatively benign nature of certain types of thyroid carcinoma and because of our small group of cases, we are unable to correlate histologic type with prognosis accurately. Long survivals in both the

papillary and the alveolar and follicular classifications were seen. The only apparent difference is that, whereas 3 of the 16 papillary cases demonstrated pulmonary metastases, 6 of the 9 cases with alveolar and follicular carcinoma showed pulmonary involvement. The one death definitely due to the disease occurred in a patient having solid carcinoma. In addition, all 4 patients with solid carcinoma developed pulmonary metastases. We feel that the prognosis is poorest in our patients with solid carcinoma. We believe also that the alveolar and follicular carcinomas would be associated with a lower survival rate than the papillary tumors if large groups of children with these neoplasms were studied.

RADIOAUTOGRAPHIC STUDIES

From 10 patients, 14 operative specimens of thyroid carcinoma were studied with radioautographic techniques (2). In the 10 cases there was concentration of radioactive iodine (I^{131}) in some portion of all operative specimens. As has been previously shown (2) the concentration of radioiodine can be roughly related to the presence of colloid in the carcinoma. In 4 cases of papillary carcinoma there was concentration of the isotope in regions where there was an admixture of follicle formation. In 3 cases of alveolar and follicular carcinoma the isotope was concentrated to a greater degree. Two cases of solid carcinoma showed good concentration of the isotope in a few areas which did show follicle formation. In 1 case which showed varying portions of papillary, alveolar, follicular, and solid carcinoma the radioiodine was concentrated quite well generally in the colloid-bearing areas and surprisingly well in the less differentiated areas.

It has been found that, in a large series of thyroid carcinoma, about 45 per cent concentrated radioiodine (2). From the radioautographic findings in these cases, one gains the impression that thyroid carcinoma in childhood or adolescence possesses greater capacity for concentrating radioiodine than histologically similar lesions in adults. Since our group, however, contains for the most part histologic types found to be receptive to radioiodine, a larger series of cases will have to be studied to demonstrate the validity of this impression.

ANATOMIC FINDINGS AND DISTRIBUTION OF METASTASES

The initial signs of disease in 10 patients were one or more enlarged cervical lymph nodes. In these 10 patients no palpable abnormality was observed in the thyroid. Sixteen patients presented both nodules in the thyroid and one or more enlarged cervical lymph nodes. In only 2 instances was a thyroid enlargement the only evidence of tumor. Carcinoma was found in the surgically removed thyroids in all cases.

Since neck dissections were done in the majority of our cases, it has been

possible to determine the extent of cervical node involvement in this group of patients. Figure 6 illustrates the anatomic classification of cervical lymphatics used at our institution. It also represents the distribution and frequency of cervical lymph node metastases in our patients. It will be observed from this chart that the deep jugular group of nodes was most commonly involved. However, in 2 cases the disease was found to be

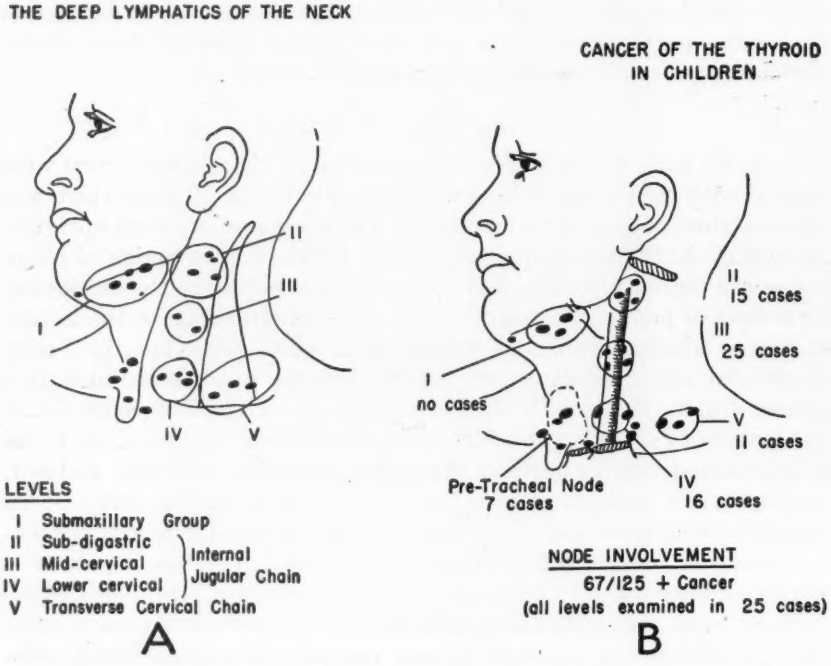

FIG. 6. Classification of cervical lymph nodes (A) and the frequency of their metastatic involvement (B) in children with thyroid cancer.

limited to the posterior cervical triangle. In tumors involving the thyroid isthmus, the pretracheal nodes were often involved. Thirteen of our 28 patients presented evidence of bilateral cervical node metastases on admission. In 2 patients cervical node involvement which was not suspected before operation was demonstrated after neck dissection.

In 13 patients, pulmonary metastases were either demonstrated on admission or were observed to develop subsequently. Eleven of these children with pulmonary metastases presented no signs or symptoms referable to lung lesions. Two, however, did present pulmonary symptoms of a troublesome nature, *i.e.*, cough or hemoptysis.

The appearance of the chest roentgenograms of those children having pulmonary metastases was in general a characteristic one. Figure 7 illustrates in 2 patients this diffuse miliary to nodular infiltration affecting primarily the basilar portions of the lungs. Large solitary lesions of the lung were rarely seen in this series of cases. There was no significant difference in the x-ray appearance of pulmonary metastases from different histologic types of thyroid cancer.

This miliary spread of pulmonary metastases was also observed in the

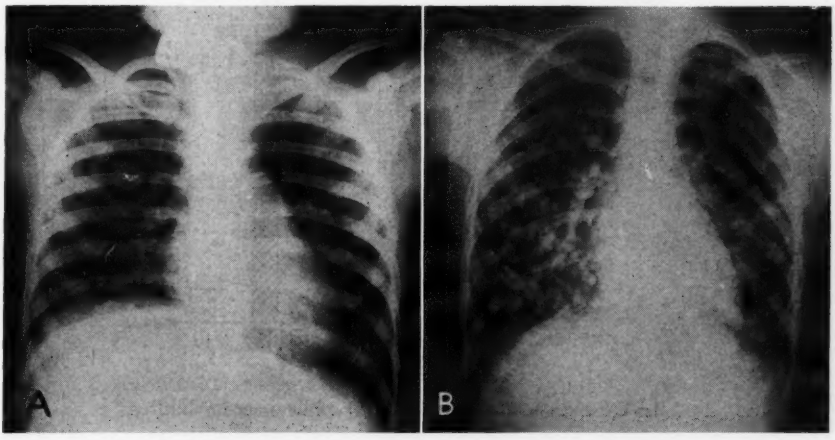

FIG. 7. The x-ray appearance of pulmonary metastases of thyroid cancer: A) early (Case 15); B) advanced (Case 16). Both patients have demonstrated I^{131} concentration in these lung lesions.

cases reported by Kennedy (3) and by Ward (4). The roentgen appearance of these lung lesions gives rise to the possibility of confusion in diagnosis. In 2 of our patients a diagnosis of tuberculosis was made, on the basis of their chest roentgenograms. In a third case the chest x-ray findings had led to the diagnosis of histoplasmosis.

Skeletal metastases have not yet been observed in this series of patients. On the other hand, in 20 per cent of the total thyroid series, metastases to bone have developed. In 1 of these patients a single metastasis to the choroid plexus was diagnosed and confirmed at craniotomy.

POSSIBLE ETIOLOGIC FACTORS

Sex and age

Of the 28 cases in this series, 16 were observed in females and 12 in males. This almost equal sex distribution should be contrasted to the ratio

of 2 females to 1 male in the complete series of thyroid cancer seen during the same period in this clinic, and to Langmann and Bruch's (5) review of this subject, in which there were 18 cases in females and only 3 in males.

The patients included in this report ranged in age from 4 to 18 years at the time of histologic diagnosis. Because of our interest in growth and general endocrine activity we have attempted to determine the age at which

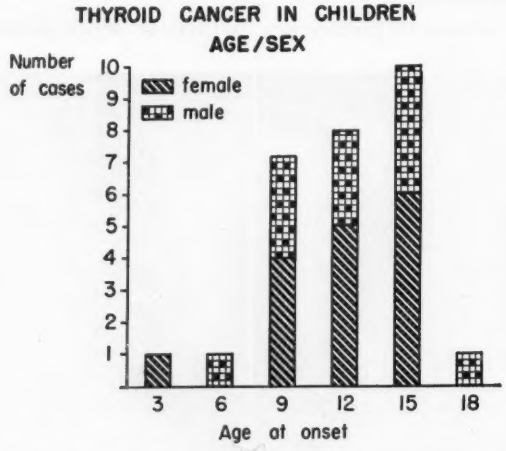

FIG. 8. Age and sex distribution of thyroid cancer in children.

the first evidence of a tumor became manifest. This is but an arbitrary figure but it may throw some light on the biology of such tumors (Fig. 8):

Age at which first signs of tumor were noted

Age, yrs.	Females	Males
3	1	—
6	—	1
9	4	3
12	5	3
15	6	4
18	—	1

From this tabulation it will be noted that although there were 2 patients under the age of 9 years, the apparent age of onset can be correlated with puberty. This correlation of onset with puberty is important in the light of Rice's (6) study on the anatomy of the human thyroid, in which it was demonstrated that the maximum increase in thyroid weight occurred with puberty and that nodules or tumors were not demonstrable before puberty. Judging from the studies by Nathanson, Towne, and Aub (7), who observed

an increase in the urinary excretion of steroid between the eighth and twelfth years (Fig. 9), the 9-year-old children could be described as early pubescents.

It is difficult to explain the development of tumors in the 2 youngest children on the basis of a physiologic stimulus to thyroid growth. As will be pointed out subsequently, however, the youngest patient came from

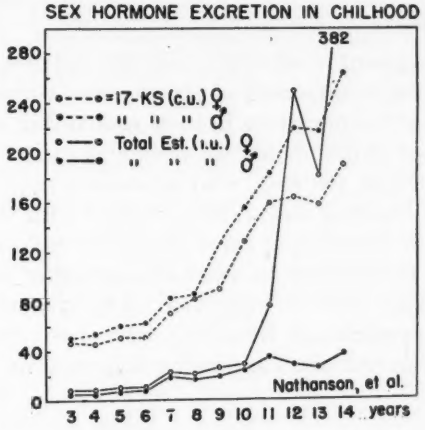

FIG. 9. Excretion of estrogen and 17-ketosteroids in childhood (from *Nathanson, Towne and Aub* (7). Courtesy, *Endocrinology*).

an endemic goiter area and both of her parents had taken desiccated thyroid for symptoms ascribed to hypothyroidism.

Environmental (geographic) and familial histories

Because of the possible relationship of endemic or sporadic goiters in patients or their families, the geographic and family histories of all of these children have been analyzed. With 1 exception, all of these patients were born within the United States. One was born in Hawaii. Only 1 of these patients came from a known endemic goiter area (Michigan).

Geographic distribution	
Northeast (Seaboard)	15
Middle Atlantic	6
South	3
Midwest (Michigan)	1
Southwest	2

We hasten to point out, however, that even on the sea coast where there is theoretically an adequate intake of iodine, sporadic or nontoxic goiters are not uncommon. Even so, a history of thyroid disease in the parents

or siblings of these patients was surprisingly low. Both parents of our youngest patient (Case 15) gave histories of having taken desiccated thyroid for hypometabolism and symptoms ascribed to hypothyroidism. In neither parent was there any evidence of goiter. The mother of another patient (Case 28) had had a thyroidectomy for Graves' disease five years prior to the birth of the patient.

Growth and development

Birth and development of all of our patients had been normal. With the exception of possible enlargement of the thymus, which will be discussed later, there were no complications in their neonatal or childhood periods.

In none of these children did we recognize other endocrine disease. Indeed, 8 of the recent patients, who have been subjected to studies or treatment with radioactive iodine, were studied with thorough and sensitive methods for the detection of hematologic and endocrine abnormalities. They were found to manifest no other abnormalities in the glands of internal secretion. This is to be contrasted to the reports of Kennedy (3), Ward (4), and Langmann and Bruch (5), who observed cancer of the thyroid in children who had other endocrine abnormalities or developmental defects.

Irradiation of enlarged thymus

There were 9 patients in this series who had been subjected to irradiation to the thymus for obstructive respiratory symptoms ascribed to "enlargement of the thymus." In all instances these were short courses of low voltage x-ray administered sometime between the fourth and eighteenth months of life.

Whether or not the thymus in these children had been enlarged, is a point that we do not choose to discuss at this time. To propose a cause-and-effect relationship between thymic irradiation and the development of cancer would be quite unjustified on the basis of data at hand when one considers the large number of children who have had irradiation to an "enlarged thymus." However, the potential carcinogenic effects of irradiation are becoming more and more apparent, and such relationships as those of thymic irradiation in early life and the subsequent development of thyroid or thymic tumors might be profitably explored.

TREATMENT

The treatment and results for each case are tabulated in Table 1.

Of the 28 patients in this series, 14 were referred to Memorial Hospital after partial thyroidectomy and/or irradiation. Nine patients were referred following biopsy. Only 5 patients had their complete diagnostic and therapeutic programs carried out in this clinic.

TABLE 1

Patient	Memorial Hospital number	Sex	Age at onset (yrs.)	Pathologic diagnosis	Treatment	Survival		Remarks
						Since onset	Since seen at Memorial Hospital	
1. W.B.	75614	M	12	Solid	Surgery	5	3	Lung metastases. Died.
2. A.B.	71728	M	15	Papillary	Surgery	7	6	Lung metastases.
3. D.B.	48700	F	10	Follicular alveolar	Surgery, X-ray	17	15	Lung and brain metastases.
4. J.C.	58559	M	8	Papillary	Surgery	9	9	No evidence of disease.
5. C.D.	78042	M	5	Papillary	Surgery	5	4	Partial thyroidectomy. No evidence of disease.
6. H.F.	52477	M	9	Papillary	Surgery, X-ray	13	13	No evidence of disease.
7. E.F.	73800	F	14	Papillary	Excision, biopsy	9	5	Refused treatment.
8. G.G.	64271	F	13	Follicular alveolar	Surgery	9	8	Glioma of retina.
9. T.G.	92891	M	9	Follicular alveolar	Surgery, I^{131}	10	1	Lung metastases. Improved on I^{131}
10. E.G.	86167	F	12	Follicular alveolar	Surgery	6	2	Lung metastases.
11. N.J.	76485	M	15	Papillary	Surgery	5	4	Left cord paralysis.
12. D.K.	89431	F	10	Solid	Surgery, I^{131}	4	2	Lung metastases.
13. L.K.	Clinic	F	9	Hürthle	Surgery	2	1	No evidence of disease.
14. G.K.	S7905	F	12	Papillary	Surgery	12	13	Refused treatment. Pregnancy. Died.
15. N.L.	92244	F	3	Solid	Surgery, I^{131}	2	1	Lung metastases.
16. W.M.	87060	M	10	Follicular alveolar	I^{131}	4	2	Lung metastases. Improved on I^{131}.
17. E.M.	79662	F	8	Papillary	Surgery	5	4	No evidence of disease.
18. W.M.	86894	M	14	Follicular alveolar	Surgery, I^{131}	4	1	Lung metastases.
19. E.M.	Clinic	M	16	Papillary	X-ray	15	14	No evidence of disease following x-ray treatment.
20. B.M.	48806	F	15	Papillary	X-ray, surgery	16	13	Lung metastases for past 12 years.
21. M.M.	96790	F	15	Papillary	Surgery	2	6 mos.	No evidence of disease.
22. F.M.	89770	F	9	Papillary	Surgery, I^{131}	5	1	Lung metastases.
23. J.P.	95121	F	8	Solid	Surgery, I^{131}	2	6 mos.	Lung metastases.
24. W.R.	83637	M	13	Papillary	Surgery, X-ray	8	3	No evidence of disease.
25. M.S.	84004	F	15	Follicular alveolar	Surgery	4	3	No evidence of disease.
26. R.T.	52701	M	14	Papillary	Surgery, X-ray	13	13	Recurrence in neck.
27. V.T.	82153	F	10	Papillary	Surgery	10	3	No evidence of disease.
28. D.Y.	88506	F	10	Follicular alveolar	Surgery, I^{131}	3	2	Lung metastases.

Seventeen of our patients were treated by complete thyroidectomy and neck dissections. In 11 patients who had metastases to the bilaterial cervical nodes, the neck dissections were done in two stages. We administered postoperative irradiation to only 4 of our patients.

To date there have been only 2 deaths in this series. However, since we have been able to follow only 6 of our patients for ten years or more, we are unprepared to discuss the effects of treatment on this series of patients.

Notwithstanding the fact that the mortality rate in this series is apparently low, the morbidity is impressive, *i.e.*, bilateral neck dissections, lung metastases, and persistent disease. We believe that in view of the aggressive nature of this disease in the children that we have studied, enlarged cervical

nodes or nodules in the thyroid when seen in children should be viewed with suspicion until the diagnosis of cancer of the thyroid has been ruled out.

SUMMARY

Twenty-eight cases of thyroid cancer observed in children under the age of 18 years have been reported and described.

The histologic types included papillary carcinoma—15 cases; alveolar and follicular carcinoma—8 cases; solid carcinoma—4 cases; and unclassified carcinoma—1 case.

All but 2 of the patients had metastases in the cervical lymph nodes. In 10 patients the only presenting evidence of disease was one or more enlarged cervical lymph nodes.

Pulmonary metastases were observed on admission or subsequently in 13 patients.

The age of onset was correlated with puberty in 25 cases.

Only 1 patient came from an endemic goiter area; only 2 gave a familial history of thyroid disease.

Nine of the patients had been submitted to low voltage x-ray therapy for "enlarged thymus" between the fourth and eighteenth months of life.

It has been emphasized that thyroid cancer should be seriously considered in the diagnosis of "lumps" in the necks of children.

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SIMPLE GOITER IN COLOMBIA

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IN HIS paper of this title, Parra (1) mentioned the recent increase in the incidence of goiter in the Departments of Caldas and Antioquia and stated: "This has been due to the fact that the regional consumption of salt from iodized sources has been almost completely replaced by the use of salt from the large mines near Bogota." He gave no figures for the iodine content of these salts but in a letter dated March 17, 1949, he stated that the "salts from iodized sources" were from Guaca in Antioquia and from Bella Vista in Choco, and contained 4 and 35 mg. respectively, per 100 Gm. of salt. The iodine content of the salt from "the large mines near Bogota" is said to be "from 2 to 3 tenths milligram per 100 Gm. of salt."

According to this information, the concentration of iodine in the salts from Guaca and Bella Vista are, respectively, 8 and 70 times as great as the highest previously recorded and are 33 and 292 times as much, in proportion to chloride, as is found in sea-*water*. (Sea *salt* contains much less (2).)

It is possible, even probable, that there was no significant amount of goiter in Colombia as late as 1740 (3). By 1760 or 1762, it seems to have been prevalent throughout the upper Magdalena valley (4) (5). However, Mutis, to whom we owe this evidence, is also on record as stating that the disease was very recent in Bogota in 1794 (6). The same statement was made by Humboldt (7).

When these facts were sent to Dr. Parra, he replied: "At the end of the XVII (*sic*) Century, when Humbolt visited Colombia, improvements were beginning in the means of land transportation to Bogota. This fact brought about the arrival in Bogota of people from those provinces which were particularly known for the high incidence of simple goiter. The road from Honda to Bogota was the only communication with the Magdalena River. This road crossed through a geographic zone in which for more than a century there was also a very high incidence of simple goiter."

There is no evidence, however, that goiter had been present anywhere in Colombia "for more than a century" before Humboldt's visit nor is there any evidence that Humboldt and Mutis did not distinguish between goiter in recent arrivals in Bogota and a true increase in the incidence of the disease.

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As elsewhere, the incidence of goiter in Colombia has shown remarkable increases and decreases. Thus, in 1900, Marquez wrote (8) "In Bogota, it was so abundant at the beginning of the last century that it appeared to Caldas that the capital would be condemned to a population of goitrous people if the increase in goiter continued at the rate existing at that time. Today, goiter is rare, though not exceptional, in Bogota. . . . As soon as use was had of river water, goiter began to diminish and, today when the population is provided with running water from aqueducts, one can say that the disease has disappeared." (Trans., I.G.)

("En Bogotá era muy abundante hasta principios del siglo pasado, hasta tal punto que para Caldas la capital estaba condenada á ser una poblacion de cotudos si el aumento del Coto seguia en la proporcion en que exista

TABLE 1. PERCENTAGE OF GOITERS IN MEN OF MILITARY AGE
(Data from Socarras (9))

Department	Year					
	1935	1936	1937	1938	1939	1940
Antioquia	—	0.28	0.15	0.62	0.66	1.20
Boyaca	3.61	9.59	5.86	5.51	8.06	8.86
Caldas	11.41	9.15	11.30	16.58	10.39	23.89
Cundinamarca	3.80	2.13	1.83	16.23	19.32	11.61
Narino	12.14	9.13	9.53	11.11	11.10	7.06
Santander	7.60	15.31	14.55	8.73	10.14	8.38
Tolina	5.67	20.51	21.62	38.18	18.41	21.96
Valle	9.32	17.19	15.27	23.14	21.33	16.75

en esa época. Hoy el Coto es raro, sin ser excepcional, en Bogotá. . . . Tan pronto como comenzo a hacerse uso de aguas corrientes de rio comenzo á disminuir el coto, y hoy, cuando la poblacion está provista de agua corriente por medio de acueductos, puede decirse que ha desaparecido la enfermedad.")

Bogota is in the Department of Cundinamarca and the statement by Marquez is in harmony with the figures for the frequency of goiter in men of military age published by Socarras in 1942 (9). Table 1 gives the percentage of goiters among the men arriving at military age in several of the Departments of Colombia from 1935 to 1940. The low figures for Cundinamarca in 1935, 1936, and 1937 and the sudden increase in 1938 are very striking. The increases in Antioquia and Caldas were no more marked.

The history of goiter in Colombia, as elsewhere (3) (10) (11) is that of an infectious disease, which may become endemic or may disappear, sometimes recurring to the confusion of those who ignore local history.

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Endocrine Review

THE BIOLOGIC PROPERTIES OF CORTISONE: A REVIEW

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THE word "cortisone" is a name introduced by Dr. E. C. Kendall of the Mayo Foundation to identify a compound which has previously been referred to as 17-hydroxy-11-dehydrocorticosterone or as "Kendall's compound E."

Cortisone was isolated in crystalline form from extracts of beef adrenal glands in 1935. The isolation and characterization of its general physical and chemical properties was accomplished independently by Mason, Meyers and Kendall (1), Wintersteiner and Pfiffner (2) and Reichstein (3). A partial synthesis of cortisone from desoxycholic acid has been realized by Sarrett (4). Sufficient amounts of cortisone are now available to permit extensive laboratory and clinical investigations of its properties. The production of cortisone is expensive and limited by the availability of starting materials. However, recent developments offer hope that these restrictions will be overcome in the future.

This review will be concerned with A) the physiologic effects of cortisone and B) its use in the treatment of diseases.

PHYSIOLOGY

1. Maintenance of life

Relatively large doses of cortisone are required to maintain life in adrenalectomized animals. Indeed, when Wintersteiner and Pfiffner (2, 5) first isolated this compound, it was characterized as physiologically inactive on the basis of its failure to sustain life in adrenalectomized dogs. When the compound was isolated in the Mayo Foundation laboratories in 1935, it was found to be biologically active in the muscle-work test of Ingle (6) and subsequently Dr. W. D. Allers at the Mayo Foundation Institute for Experimental Medicine demonstrated that large doses of cortisone, in the absence of other treatment, would sustain life in adrenalectomized dogs. Kendall (7) has reported that a dose of 10 mg. of cortisone daily is required to sustain an adrenalectomized dog. Kuizenga and Cartland (8) found that cortisone would sustain life in immature adrenalectomized male rats, but that larger amounts were required than of 11-desoxycorticosterone acetate or noncrystalline preparations of adrenal

cortex extracts. These early observations on the high dosage requirements of cortisone led to the belief that it was a physiologically unimportant compound, and its identification was welcomed principally because it provided evidence regarding the chemical nature of adrenal cortical hormones.

The value of cortisone in the treatment of Addison's disease is now established and will be discussed later, but, insofar as the author is aware, the dosage range required for the maintenance of life in adrenally insufficient patients without other forms of therapy has not been published.

2. Ability to work and to resist other forms of stress

Since untreated adrenalectomized animals and patients with Addison's disease show progressive deterioration leading to death, it is not surprising that adrenal insufficiency is characterized by asthenia and less-than-normal resistance to every type of stress. It is of special significance that cortisone and other 11-oxygenated compounds are relatively weak in life maintenance activity as compared to 11-desoxycorticosterone and the "amorphous fraction" but that cortisone is more potent than 11-desoxycorticosterone or the "amorphous fraction" in sustaining the ability of the adrenalectomized animal to resist stress.

When cortisone was isolated in The Mayo Foundation Laboratories in 1935, the author demonstrated it to be biologically active in the muscle-work test. The choice of the muscle-work test was fortunate but fortuitous. Its use was rationalized on the grounds of economy of time and test materials. The fact that the work test is highly specific for the 11-oxygenated adrenal steroids was not appreciated by the author until 1938. Rats were anesthetized with a barbiturate and adrenalectomized. Immediately following adrenalectomy, the gastrocnemius muscle was weighted with 100 grams and stimulated to contract three times per second until death of the animal, or for forty-eight hours. It was found that a dose of 1 mg. of cortisone given at the beginning of stimulation and repeated at 12-hour intervals was sufficient to support a normal output of work and to prevent a rise in blood urea (6). During these initial studies, the compound was administered in water solution, 0.2 mg. per cc. After a few months, it was found that when the compound was administered in oil solution, the dosage requirement was reduced to about 0.25 mg. per dose under the same conditions. This test was subsequently modified and standardized for quantitative bioassay (9).

The effect of cortisone upon the ability of the adrenalectomized rat to sustain work has been compared to the efficacy of other adrenal steroids (10–14). Cortisone is more potent than 11-desoxycorticosterone, corticosterone and 11-dehydrocorticosterone but is less active than 17-hydroxycorticosterone. Although about five hundred times more cortisone than

"amorphous fraction" is needed to sustain life and "renal function" in the adrenalectomized dog (15), cortisone is more potent than the "amorphous fraction" in its effect upon work (16). Cortisone has a similar relationship to 11-desoxycorticosterone; the latter compound is potent in supporting growth in the young adrenalectomized rat but is weak in its effect upon work performance (11). However, when cortisone by itself or in combination with 11-desoxycorticosterone (1:1 ratio) was administered to adrenalectomized rats for one or two weeks prior to the work test, the total work output was not better than 60 per cent of normal at any dosage level (11).

The effects of the adrenal steroids on work performance in the Everse de Femery test (3, 17) differ from those obtained in the Ingle test. In the Everse de Femery test, 11-desoxycorticosterone was the most active compound and cortisone was ineffective in the doses tested. This apparent discrepancy has led to some confusion in interpreting the significance of "fatigue" tests in general. Actually the two tests are different in principle. The Ingle test requires continuous stimulation over many hours, whereas the Everse de Femery test determines the extent of recovery from a brief period of stimulation and does not measure the capacity of the animal to resist a severe and prolonged stress.

Cortisone is stated to be highly effective in protecting adrenalectomized rats against typhoid vaccine (15), whereas 11-dexosycorticosterone is ineffective (18). Lewis and Page (19) have confirmed the protective action of cortisone in adrenalectomized rats given typhoid vaccine. Kendall (20) has noted that cortisone protects the young adrenalectomized rat against the stress of cold. Grattan and Jensen (21) found that cortisone and other 11-oxygenated compounds protected nonadrenalectomized mice against convulsive doses of insulin. Ingle (22) tested the effect of cortisone upon the survival of nonadrenalectomized rats subjected to the shock of limb ligation. The results were negative.

Selye (23) found that the anaphylaxis-like reaction of the rat to parenteral administration of egg white was inhibited by the administration of cortisone acetate. Elsewhere Selye (24) has shown that pretreatment with cortisone acetate prevents the initial edema and the later chronic "arthritis" caused by injection of irritants such as formaldehyde in the vicinity of joints in the rat.

Dougherty (25) and Dougherty and Dougherty (26) have studied the effect of cortisone acetate in inhibiting the hypersensitivity reactions of the adrenalectomized mouse. These animals were sensitized with horse serum, and the mortality following a challenging dose of serum was determined with and without the administration of cortisone acetate. Cortisone acetate gave prolonged protection. There was a graded relationship be-

tween the size of the challenging dose of serum and the amount of the steroid required to protect the animal. The acute and chronic inflammatory processes of cardiovascular and other connective tissues resulting from horse serum hypersensitivity are alleviated by cortisone acetate but enhanced by 11-desoxycorticosterone acetate. It was postulated that cortisone in some way alters the amount or inhibits the action of the substance or substances which cause inflammation, and that this is the basis of the favorable therapeutic effect of this steroid in the mesenchymal diseases. Further studies by Dougherty and Schneebeli (27) have demonstrated that cortisone acetate inhibits the acute inflammatory reaction to topical allergy in adrenalectomized mice.

Stoerk (28) found that in guinea pigs vaccinated with heat-killed human tubercle bacilli, the tuberculin reaction could not be elicited when cortisone acetate was administered prior to the injection of old tuberculin. In further studies, it was found that hypersensitivity of the anaphylactic type was not prevented by cortisone acetate in guinea pigs. In the Arthus reaction, cortisone acetate administration reduced the amount of fluid exudation, but not the cellular infiltration in the tissues. The amount of necrosis and hemorrhage was not significantly diminished. Smith, Smith and Thompson (29) found that cortisone acetate was without effect upon the mortality, survival time, weight and hematologic changes in irradiated nonadrenalectomized mice.

Although a number of clinical investigators have expressed the opinion that the vigor and resistance of patients with Addison's disease are improved by the administration of cortisone, no objective data have been published. Sprague (30) has described studies of muscle efficiency in patients with Addison's disease before, during and following the administration of cortisone acetate. The results indicated that cortisone acetate increased the capacity for work. On the other hand, it has been noted (31) that the prolonged administration of large doses of cortisone acetate (100 mg. and more per day) was associated with the development of muscular weakness in some patients having rheumatoid arthritis. Muscular weakness occurs frequently among patients with Cushing's syndrome, a disease which is thought to represent hypercorticism.

3. Electrolyte and water metabolism

The effect of cortisone upon electrolyte balance is variable. The results are affected by dosage, time of administration, species and possibly by other variables not yet studied. In acute experiments on the rat, it was shown by Thorn, Engel and Lewis (32) and by Ingle and Thorn (33) that cortisone and 17-hydroxycorticosterone both cause an increase in the excretion of sodium, chloride and potassium. Similar results were obtained

in the dog by Lewis, *et al.* (34). It was subsequently found by Ingle, *et al.* (35, 36, 37) that the increase in the excretion of sodium and chloride was temporary (lasting from one to three days) and that a normal balance was quickly restored. The increased excretion of potassium was sustained for longer periods of time. In studies of rats given rabbit anti-rat kidney serum and subsequent injections of cortisone acetate (2.5 mg. daily) for four to five weeks, Knowlton *et al.* (38) noted small increases in serum sodium in both nonadrenalectomized and adrenalectomized animals. Woodbury and Sayers (39) have studied the effect of cortisone acetate (2 mg. daily for thirty-seven days) on the electrolyte metabolism of the unilaterally nephrectomized rat given 0.9 per cent sodium chloride to drink. The concentrations of sodium, potassium and chloride in plasma and muscle of animals treated with the steroid are not significantly different from those of control unilaterally nephrectomized rats given 0.9 per cent sodium chloride to drink. Lewis *et al.* (34) gave a single injection of 25 mg. of cortisone to 1 normal and to 1 adrenalectomized dog. No changes in the sodium, chloride and potassium content of serum were noted. It is known that in the dog and other animals a negative sodium balance develops following adrenalectomy. Large doses of cortisone will sustain life in adrenalectomized dogs. Probably life-maintenance doses of cortisone can correct the negative sodium balance of such animals, but no data have been reported.

Although 11-desoxycorticosterone is more potent than any of the 11-oxysteroids in affecting electrolyte balance, it is less potent than cortisone in stimulating diuresis in acute tests and in preventing water intoxication (40). One milligram of cortisone is equivalent to 3 milligrams of 11-desoxycorticosterone acetate in maintaining diuresis and preventing toxic symptoms in the adrenalectomized rat under a high water load.

The effects of cortisone and other 11-oxysteroids upon electrolyte balance in man are much less marked than the effects of 11-desoxycorticosterone. Thorn *et al.* (41, 42) found the effects of cortisone acetate upon sodium and chloride excretion in patients with Addison's disease to be small and variable. It was concluded that large doses (100 mg. daily) may cause slight sodium, potassium and chloride retention when given without other therapy, but that the addition of cortisone acetate to a basic dose of 11-desoxycorticosterone acetate fails to cause sodium and chloride retention and may cause a rise in urinary sodium. Perera *et al.* (43) reported that cortisone acetate in doses of 80 mg. daily caused a small to moderate retention of sodium, chloride and water with a slight drop in the concentration of serum sodium. In 1 patient with Addison's disease, there was a transitory increase in the excretion of sodium, chloride and water followed by retention. Sprague *et al.* (31) described the effects of large doses of

cortisone acetate in patients with rheumatoid arthritis and related diseases. In doses of 100 mg. daily for twelve to thirty days, cortisone acetate had little or no effect upon the balances of calcium, sodium, chloride and potassium and upon the concentrations of these ions in blood. Cortisone acetate in doses of 200 mg. daily for twelve to eighteen days caused a negative potassium balance. The changes in sodium and chloride excretion were variable, but there was generally a retention of these ions followed by a rise in excretion. This higher dose of cortisone acetate caused a hypochloremic, hypokaliemic alkalosis which was identical with that seen in some patients with Cushing's syndrome. The administration of cortisone acetate caused edema in some of the patients. When the injection of the steroid was stopped, the electrolyte balance reverted to normal.

Conn (44) administered cortisone acetate to patients with rheumatoid diseases and found a decrease in the concentration of sodium and chloride in sweat beginning on the fifth or sixth day after the initiation of treatment, as compared to a fall on the second day of treatment with 11-desoxycorticosterone acetate. The decrease in the sodium and chloride concentrations of sweat was much greater with 10 mg. of 11-desoxycorticosterone acetate than with 200 mg. of cortisone acetate per day.

4. Circulation

There have been few reports on the effects of cortisone upon circulation in experimental animals. In the opinion of the reviewer, this should be a fruitful field for intensive investigation; there is a paucity of information about the relationship of adrenal cortex function to cardiac output, cardiac efficiency, circulation time, blood flow, etc.

Swingle and associates (45) have shown that cortisone and corticosterone are very effective in maintaining circulatory adequacy in adrenalectomized dogs subjected to intestinal or muscle trauma, surgery or hemorrhage. Guadino (46) found that experimental renal hypertension in the rat was not sustained following adrenalectomy but reappeared during injections of cortisone. Knowlton *et al.* (38) produced cytotoxic serum nephritis in the rat. The renal changes were not prevented by the administration of cortisone acetate. When nonadrenalectomized nephritic rats were injected with cortisone acetate (2.5 mg. daily), a moderate hypertension developed, whereas similar treatment of adrenalectomized nephritic rats caused a severe hypertension. The authors suggest that other adrenal steroids produced by the nonadrenalectomized rat may counteract the pressor effect of cortisone. Another possible explanation for these and similar results is that the adrenal cortices may have the ability to inactivate an excess of cortical steroids as well as to carry out biosynthesis. Selye (47) has also observed that the administration of cortisone acetate

to the unilaterally nephrectomized rat on a high sodium, high protein diet causes elevation in blood pressure associated with renal damage. Very little cardiac damage was noted. Cortisone acetate did not inhibit the pressor effect of 11-desoxycorticosterone acetate in the rat.

In human subjects, Perera *et al.* (43) found that cortisone acetate had a small depressor effect on the "resting" blood pressure of 2 hypertensive patients and increased the subnormal pressure of a patient with Addison's disease. The dose was 80 mg. daily in each patient. In a series of 27 patients having rheumatoid arthritis or related diseases, Sprague *et al.* (31) noted a definite effect of cortisone acetate upon blood pressure in only 1 case. A woman who was severely ill with disseminated lupus erythematosis showed marked clinical improvement during treatment with cortisone acetate but showed a significant rise in blood pressure. When the administration of the steroid was stopped, the blood pressure fell to pretreatment levels. There was evidence that this patient had antecedent parenchymatous renal disease. In describing the same series of patients, Hench *et al.* (48) noted that 3 patients showed a slight rise in systolic pressure (10 to 30 mm.) when 200 mg. of cortisone acetate was given daily.

5. Permeability

A number of investigators have found evidence that adrenal cortical insufficiency, adrenal cortex extracts and certain steroids can influence the permeability of membranes (49). Netsky and Jacobs (50) studied the effect of cortisone upon the mammalian red cell. Cortisone, the "amorphous fraction" and the sodium salt of the phosphate ester of 11-desoxycorticosterone each decreased the time required for the glycerol hemolysis of beef cells at all pH levels. Cortisone did not produce sphering of human erythrocytes as did certain "highly polar: non-polar" derivatives of 11-desoxycorticosterone. Hyman and Chambers (51) noted that adrenal cortex extracts and certain steroids reduced the rate of edema formation in perfused frog legs. The compound, 11-dehydrocorticosterone, was the most effective, followed by 11-desoxycorticosterone. Cortisone was weakly active, its effect being slightly greater than that of strophanthin.

More recently, Opsahl has reported effects of adrenal cortical insufficiency, adrenal cortex extracts and steroids upon the spreading action of hyaluronidase. In studies upon mice (52), it was found that the dermal spread of India ink was enhanced by adrenalectomy, whereas the administration of adrenal cortex extracts to either normal or adrenalectomized mice inhibited spreading. The compound, 11-desoxycorticosterone acetate, was without effect. It was also found (53) that adrenal cortical extracts inhibit the intradermal spreading of India ink enhanced by hyaluronidase in rabbits. In a further study (54) of pure steroids in both mice

and rabbits, it was found that cortisone acetate, and to a lesser extent, 11-dehydrocorticosterone, inhibits the spreading of intradermally injected India ink enhanced by hyaluronidase. Testosterone, estradiol benzoate, progesterone and pregnenolone had no definite influence upon the spreading action of hyaluronidase.

Winter and Flataker (55) studied the effects of cortisone acetate and other steroids upon the spreading action of hyaluronidase in rats and mice. The dye T-1824 was given both with and without hyaluronidase by intradermal injection. Adrenalectomy increased the rate of spread in mice, but adrenalectomized rats maintained in good condition by drinking 1 per cent saline showed little change from normal until the saline was withdrawn and the animals were fasted. In both rats and mice, with and without adrenals, cortisone acetate injected intramuscularly prior to the test inhibited the spreading action of hyaluronidase. Spreading was inhibited when adrenal cortex extract was mixed directly with the dye, but cortisone acetate was ineffective when injected locally. A number of other steroids were also found to inhibit the spreading factor, and the conclusion was reached that no clear relationship has been established between chemical structure and the spreading factor.

Seifter, Baeder and Dervinis (56) observed that hyaluronidase reversibly accelerates osmosis and abolishes the semipermeable nature of membranes prepared from the excised bladder of rabbits. Adrenal cortex extract and estrone antagonized the effect of hyaluronidase upon the permeability of bladder membranes, whereas 11-desoxycorticosterone enhanced the action of hyaluronidase. In a further study of the effects of hyaluronidase and steroids upon permeability (57), phenolsulphonphthalein was injected into the joint of a rabbit, and its speed of absorption through the synovial membrane was measured by determining the time and rate of its excretion into the urine. Hyaluronidase markedly increased the permeability of the synovial membrane. The compound, 11-desoxycorticosterone acetate, increased permeability, but when given in addition to hyaluronidase, there was no additive effect. Cortisone acetate and to a lesser extent adrenal cortex extract and estrone were effective in decreasing the permeability of the synovial membrane. Seifter *et al.* (58) have found that a number of steroids in addition to cortisone acetate inhibit the effects of hyaluronidase and of 11-desoxycorticosterone acetate upon the permeability of the synovial membrane. These substances are considered to affect permeability by acting upon the hyaluronate of the ground substance of the membranes.

The antagonistic action of cortisone acetate to the effect of hyaluronidase upon permeability is of special interest since there is evidence that hyaluronidases may play a role in the pathogenesis of rheumatoid arthritis by attacking the synovial structures (59). The significance of this relationship

is confused by the fact that a number of steroid and nonsteroid compounds inhibit the action of hyaluronidase (59, 60). The question as to whether measurement of the antihyaluronidase activity of compounds could be used as a method of predicting their possible usefulness in the treatment of rheumatoid arthritis and related diseases in patients is now under investigation in a number of laboratories and clinics.

6. Organic metabolism

a. Growth and nitrogen balance. When immature adrenalectomized rats are treated with cortisone in doses of 0.25 to 1.0 mg. daily, they are able to survive and grow but at a subnormal rate (8, 61). Larger doses of cortisone inhibit growth in immature normal rats (62). Cortisone fails to sustain growth in young, sexually mature adrenalectomized rats at any dosage level (11, 16, 63). Large doses of cortisone (1 to 5 mg. daily) may cause a negative nitrogen balance in the rat, but the peak of nitrogen loss is not sustained. On doses of 1 to 2 mg. daily, the young rat is able to re-establish a positive nitrogen balance and gain some weight (64). Winter *et al.* (65) administered 3 mg. of cortisone acetate daily to young male rats for a period of six weeks. Growth ceased during this period. The rats treated with the steroid consumed 47 per cent more food than a control group having the food intake regulated to maintain the same body weight as the injected animals. When the injections were stopped, growth was resumed.

Addis, *et al.* (66) found that the normal rat responds to the injection of hog renin by developing an intense proteinuria. This response is slight in the adrenalectomized salt-maintained rat, but the ability to mobilize and excrete protein is restored to normal by treatment with 1 mg. of cortisone acetate daily. Clark (67) administered 3 mg. of cortisone acetate daily to normal and adrenalectomized rats. On the fourth day the animals received a tracer dose of glycine containing N15. Cortisone acetate markedly increased urinary nitrogen, more so in the adrenalectomized rats than in the normal ones. The accompanying increased excretion of the isotope indicated that cortisone acetate suppressed protein synthesis. These data are pertinent to the hypothesis of Albright (68) that cortisone and the other11-oxygenated steroids of the adrenal cortices have an "anti-anabolic" effect rather than a "catabolic" effect. Hoberman (69) administered cortisone acetate before and after the injection of isotopic glycine in adrenalectomized and in adrenalectomized-thyro-parathyroidectomized rats. Cortisone accelerated the metabolism of amino acids and caused a marked increase in the rate of protein breakdown in both groups of animals. There was a concomitant diminution in the rate of conversion of amino acids to protein, more marked in the hypothyroid animals than when the thyroid gland was present.

Karnofsky, Stock and Rhoads (70) injected cortisone acetate into the yolk sac of the 4-day chick embryo. At a dose of 1 to 2 mg. per egg, there was a marked retardation of the growth of the embryo. The compound, 17-hydroxycorticosterone, was much more potent in stunting the embryo under these conditions. Karnofsky (71) has also demonstrated that cortisone acetate and 17-hydroxycorticosterone inhibit the growth of the young chick.

Whitaker and Baker (72, 73) noted that the percutaneous application of cortisone had a local inhibitory effect upon the growth of hair. Baker and Castor (74) studied the cutaneous atrophy induced by the percutaneous application of a highly concentrated extract of adrenal cortex in the rat. Following cessation of hair growth, thinning of the epidermis occurred. There was a reduction in size of the epidermal cells. There was atrophy of the collagenous fibers accompanied by a reduction in cellularity of the connective tissue. The elastic fibers were not reduced by the treatment. It was concluded that the 11-oxygenated steroids may act directly on the protein of intercellular structures and the epithelial cells. Cessation of hair growth was also observed by Winter *et al.* (65) during the subcutaneous administration of 3 mg. of cortisone acetate daily in the young male rat.

Schneebeli (75) has noted specific alterations in the fibroblasts of loose connective tissue following the administration of cortisone acetate to adrenalectomized mice. There were changes in the amorphous ground substance and striking alterations in the fibroblasts four hours after the administration of cortisone acetate. These cells contained large acidophilic cytoplasmic inclusions. Blunt *et al.* (76) administered cortisone acetate (25 mg. daily) to rabbits for three days prior to fracturing of the femur and thereafter until the animals were killed. Up to the fourth post-fracture day, the inflammatory and reparative responses of connective tissue were the same in both control and cortisone-treated animals. After this time, there was retardation of all phases of healing in the cortisone-treated animals. New blood vessels were more numerous in the control animals.

Ragan and associates (77) reported that the intramuscular injection of 12.5 mg. of cortisone acetate twice daily in the rabbit inhibited the granulation of wounds. Ragan and other associates (78) have noted a delay in the granulation of wounds of patients during treatment with large doses of cortisone acetate and adrenocorticotropic hormone. Similar inhibitory effects on granulation in response to injury have been reported by Selye (24) and by Taubenhaus and Amromin (79) who administered cortisone acetate to rats with turpentine abscesses. Cortisone acetate had an inhibitory effect upon fibroblasts, caused the appearance of increased numbers of macrophages and inhibited collagen formation. Baker (80) has shown that the direct application of cortisone to the wound inhibits granu-

lation. It is important to note this evidence of a direct action upon growth processes which does not require mediation of action by other organs. The observations on the inhibition of the growth of granulation tissue may be of special significance in elucidating the mechanism of the therapeutic effect of cortisone in the "mesenchymal diseases" in man.

Cortisone also inhibits the growth of tumor tissues under certain conditions. Heilman and Kendall (81) found that cortisone caused rapid and complete regression of a transplantable lymphosarcoma in the mouse, but that the tumors usually recurred and became refractory to treatment. Emerson, Wurtz and Zanetti (82) observed regression of lymphosarcoma transplants following the administration of cortisone acetate to riboflavin-deficient mice. When the same dose of cortisone acetate (0.5 mg. day) was given to mice on a stock diet, only a transient retardation of tumor growth occurred and the animals died. Baker and Whitaker (83) produced carcinomas of the skin by the local action of 3-methylcholanthrene in mice. The direct application of solutions of cortisone inhibited the growth of the neoplasms. Ingle, Prestrud and Rice (37) found that the injection of 5 mg. of cortisone acetate daily retarded but did not completely suppress the growth of the Walker carcinoma in force-fed rats. Ingle, Nezamis and Morley (84) obtained similar results by administering 5 mg. of cortisone acetate daily to force-fed rats which bore a transplantable lymphosarcoma. Higgins, Woods and Bennett (85) found that the administration of 1 mg. of cortisone acetate daily completely inhibited the growth of transplanted rhabdomyosarcomas in mice. When the administration of the steroid was stopped, the tumor implants began to grow. Reinstitution of cortisone acetate therapy inhibited the growth of the tumors but did not cause regression. In the studies of Sugiura *et al.* (86), cortisone acetate caused a marked inhibition of the growth of rat sarcoma R39, of both the Patterson and Mecca lymphosarcomas in mice, and both the Wagner and Ridgway osteogenic sarcomas in mice; the steroid induced slight inhibition of mouse sarcoma T241 and had no effect upon sarcoma 180, adrenocarcinoma EO771 or the Harding-Passey melanoma. Burchenal, Stock and Rhoads (87) tested the chemotherapeutic effect of cortisone acetate against transplanted mouse leukemia. Although the steroid inhibited the leukemic infiltration of the liver and caused a fall in leukocyte count, it did not prolong the times of survival.

In human subjects the effects of therapeutic doses of cortisone upon nitrogen balance have not been striking. Sprague *et al.* (31) found little or no augmentation of nitrogen excretion with a dose of 100 mg. daily of cortisone acetate, but the increase was pronounced with a dose of 200 mg. daily. The accompanying creatinuria and increased excretion of uric acid provided additional evidence for increased protein breakdown in these

patients. Perera *et al.* (43) found that the administration of 80 mg. of cortisone acetate per day to 4 patients caused a negative nitrogen balance in 2 of them. Thorn and Forsham (41) also found that the changes in nitrogen excretion were small or negligible during the administration of 100 mg. of cortisone acetate daily to patients with Addison's disease. There was a small increase in uric acid excretion. In studies on normal subjects, Conn (44) has observed that 200 mg. of cortisone acetate daily produces a sustained increase in urinary uric acid with an accompanying small decrease in blood glutathione. Lazarow and Berman (88) noted a significant drop in the level of blood glutathione following the injection of cortisone acetate in normal rats. Bishop, Garner and Talbott (89) have studied the effect of colchicine and cortisone acetate on uric acid metabolism in gout. Uric acid labeled with N15 in the 1,3 positions was injected intravenously during gouty attacks before and after therapy. The excretion of the labeled uric acid permitted a calculation of the size of the uric acid pool and its rate of turnover. In 1 patient given cortisone acetate, there was a decrease in pool size and an increase in turn-over rate of uric acid.

Pearson *et al.* (90) treated 6 patients having lymphomatous tumors with cortisone acetate and adrenocorticotropic hormone separately and in combination. Regression of the tumors occurred during treatment. Further studies (91) have shown that the remissions produced by the administration of cortisone acetate to patients with malignant diseases are temporary.

b. Carbohydrate metabolism. Long, Katzin and Fry (92) found that the glycosuria of the partially depancreatized rat could be intensified by the administration of cortisone and other 11-oxysteroids, whereas 11-desoxycorticosterone acetate was ineffective. These observations were confirmed by Ingle, (93) who noted that 17-hydroxycorticosterone was also diabetogenic. Ingle and Thorn (33) compared the effects of cortisone and 11-desoxycorticosterone acetate in partially depancreatized, force-fed rats. The administration of cortisone in doses of 1 to 5 mg. daily to either adrenalectomized or nonadrenalectomized, partially depancreatized rats caused exacerbation of the diabetes, whereas similar amounts of 11-desoxycorticosterone acetate were ineffective. Glycosuria has been induced in force-fed normal rats by the administration of 5 mg. daily of either cortisone, corticosterone or 17-hydroxycorticosterone (35, 36, 37, 94). Adrenal steroid diabetes was found to be highly resistant to insulin (35). Lazarow and Berman (88) induced glycosuria in normal force-fed rats by the administration of 5 to 10 mg. of cortisone acetate daily. In some cases, the glycosuria disappeared during the continued administration of the steroid. Rats having prediabetes produced by the injection of subthreshold doses of alloxan were more sensitive to the diabetogenic effect

of cortisone acetate. Kendall (95) reported the exacerbation of diabetes in an adrenalectomized-depancreatized dog given 10 mg. of cortisone daily. Wells (96), Wells and Kendall (97, 98) and Wells and Chapman (99) studied the effect of adrenalectomy and of replacement therapy on the course of phlorhizin diabetes in the rat. The excretion of glucose and nitrogen by fasting rats treated with phlorhizin was reduced to about 25 per cent of the original level following adrenalectomy. Glycosuria and urinary nitrogen were re-established at the preadrenalectomy level by treatment with 2 mg. daily of either cortisone or corticosterone, but 11-desoxycorticosterone acetate in doses up to 6 mg. daily was only partially effective. Similar effects of cortisone were found by Lewis *et al.* (100) in studies of phlorhizin diabetes in adrenalectomized rats and dogs and by Segaloff and Many (101) in studies on the rat.

Grattan and Jensen (21) found that cortisone and other 11-oxysteroids raised the resistance of fasting mice to convulsive doses of insulin and caused an increased deposition of glycogen in the liver. Long, Katzin and Fry (92) reported that other 11-oxysteroids are glycogenic in the rat, and Long (102) and Lewis *et al.* (34) confirmed the glycogenic effect of cortisone in the fasting rat. Additional confirmation was given by the studies of Reinecke and Kendall (103); Olson *et al.* (104, 105); Dorfman, Ross and Shipley (106); Dorfman *et al.* (107); Venning, Kazmin and Bell (108); Eggleston, Johnston and Dobriner (109) and Pabst, Sheppard and Kuizenga (14), all of whom have used the glycogenic property of the 11-oxysteroids as a basis of bioassay. These compounds have the following order of potency in the glycogen deposition test: 17-hydroxycorticosterone, cortisone, corticosterone, 11-dehydrocorticosterone and 11-desoxycorticosterone. This order of relative potency is in agreement with the results of the muscle-work test (12, 14). Wang (110) and Wang and Verzar (111) have compared the glycogenic potencies of cortisone and of 11-desoxycorticosterone acetate in adrenalectomized rats. It was claimed that the apparent higher glycogenic potency of cortisone in acute experiments was almost equalled by the 11-desoxy compound when the animals were treated for seven to fifteen days. The experimental animals studied by these investigators were not fasted prior to the sampling of tissue glycogen. Fasting or other forms of stress are essential to reveal the relative deficiency of the desoxy compound in maintaining carbohydrate stores.

Thorn *et al.* (112) administered 33 mg. of cortisone during one day to a patient with Addison's disease and observed a rise in fasting blood glucose, some decrease in glucose tolerance and an increase in the threshold at which symptoms of hypoglycemia appeared. Subsequent studies have confirmed the capacity of cortisone and of cortisone acetate to increase the carbohydrate levels in patients with Addison's disease, especially during

fasting (41, 42, 43, 113, 114). In a series of 27 patients with rheumatoid arthritis or related diseases, Sprague *et al.* (31) found that the prolonged administration of cortisone acetate in doses of 100 to 200 mg. daily caused slight inconsistent increases in the fasting blood glucose and some small decrease in glucose tolerance in 4 patients. Much more striking effects have been seen in patients having diabetes or coexisting Addison's disease and diabetes. In these patients the administration of cortisone causes exacerbation of the diabetes and a significant increase in insulin requirement (114, 115, 116).

c. Fat metabolism. The relationship of the adrenal cortex to the metabolism of fat has been reviewed by Ingle (117), Wertheimer and Shapiro (118) and Hartman and Brownell (119). Ingle and Thorn (34) observed that the exacerbation of diabetes by the administration of cortisone in partially-depancreatized and in adrenalectomized partially-depancreatized rats was accompanied by ketonuria. The ketonuria of phlorhizinized rats is decreased by adrenalectomy but can be restored by the administration of cortisone (100, 101, 120). Shipley and Fry (121) found that a 2.6 mg. dose of cortisone had no effect upon the level of blood acetone in fasted rats.

Kendall (122) implanted pellets of corticosterone, of 11-dehydrocorticosterone and of cortisone into mice. The first 2 compounds caused a marked increase in the percentage of body fat, but cortisone had little effect upon body fat although it caused a loss of protein. Antopol (123) administered large doses of cortisone acetate to normal mice and observed a decrease in body fat and in the size of the hibernating fat bodies. Winter, Stoerk and Silber (65) observed a relative increase in depot fat in rats given large doses of cortisone acetate for prolonged periods. Stoerk and Porter (124) noted that untreated adrenalectomized rats, partially starved for five days, lost approximately four times as much adipose tissue as similar rats given 2 mg. daily of cortisone acetate, although the weight loss was much greater in the cortisone group. In rats that were first starved and then adrenalectomized and permitted to eat ad libitum, the administration of cortisone acetate suppressed the weight gain but accelerated the deposition of fat. Hartman, Brownell and Thatcher (125) presented indirect evidence for the existence of an unidentified principle in adrenal extracts which affects the metabolism of fat. A fraction was prepared from adrenal cortex extracts which caused deposition of fat in the liver of adrenalectomized rats during starvation, whereas the known crystalline compounds, including cortisone, were ineffective.

Thorn *et al.* (112) administered 33 mg. of cortisone to a patient with Addison's disease and observed a depression of the respiratory quotient. This was interpreted as evidence for an increase in the proportion of calo-

ries derived from protein and fat. Sprague *et al.* (31) found no consistent effect of cortisone acetate upon the respiratory quotient in 3 patients with arthritis. The administration of cortisone to patients with coexisting Addison's disease and diabetes caused a pronounced increase in the excretion of ketone bodies (115, 126). Perera *et al.* (43) reported that 80 mg. per day of cortisone acetate caused a transitory ketonuria in some patients. Adlersberg, Schaefer and Dritch (127) studied the effect of cortisone acetate upon the serum lipid partition in man. Doses of 60 to 200 mg. daily for periods of six to seventeen days caused an elevation in the concentration of serum lipid (19 to 61 per cent) in 8 of 10 patients studied. There was a slower accompanying increase of serum cholesterol.

d. Enzymes and intermediary metabolism. Fraenkel-Conrat, Simpson and Evans (128) found that cortisone in doses of 0.3 to 0.9 mg. daily caused striking increases in the concentration of liver arginase in hypophysectomized, adrenalectomized, and to a lesser extent in normal rats. Corticosterone and 11-dehydrocorticosterone were also effective, but 11-desoxycorticosterone was without effect. Kochakian and Robertson (129) implanted 13 to 15 mg. pellets of cortisone acetate into castrated adult mice and noted a significant increase in both the liver and kidney arginase activities after two days; still further increases were noted after seven and thirty days. The compound, 11-dehydrocorticosterone, showed similar activity, but 11-desoxycorticosterone was ineffective. In acute experiments, Williams and Watson (130) found that adrenal cortex extract, corticosterone and cortisone (2 mg. dose) each caused a decrease in the phosphatase content of the diaphyses of rat femurs. The studies of Price *et al.* (131) and Cori (132) have shown that certain adrenal cortex principles enhance the inhibitory effect of anterior pituitary extract upon hexokinase, but cortisone, corticosterone and 11-dehydrocorticosterone were ineffective. The effect of cortisone upon hyaluronidase activity has been reviewed in an earlier section of this paper.

Lewis *et al.* (100) found that cortisone restored the ability of adrenalectomized phlorhizinized rats to form glucose from lactic and pyruvic acids and from alanine. Wells and Kendall (98) have suggested that such effects of cortical hormones were a reflection of a general improvement in the vigor of the animal rather than to a primary action of the cortical hormones upon the formation of glucose, since in their experiments adrenalectomized phlorhizinized rats were able to form the expected amount of glucose from fed protein. Awapara, Marvin and Wells (133) studied the effect of cortisone upon the quantitative relation between the concentration of certain amino acids in liver and muscle and the level of liver glycogen in the adrenalectomized rat. Glycogen synthesis was accompanied by a relative increase in the proportion of alanine to the dicarboxylic amino acids in

liver. It was suggested that the acceleration of glycogen synthesis by cortisone may have been accomplished through the aminopherase (transamination) mechanism. According to Umbreit and Tonhazy (134) proline oxidation of rat kidney homogenates is decreased following adrenalectomy and can be restored to normal by treatment of the animal with 0.5 to 1.0 mg. of cortisone acetate daily. Adrenalectomy and cortisone treatment did not affect the ability of kidney homogenates to oxidize glutamate or other members of the tricarboxy acid cycle but appeared to affect the concentration of the proline oxidizing enzyme. From their studies showing that adrenal cortical activity affects the metabolism of fat as well as carbohydrate and protein, Stoerk and Porter (124) postulate that adrenal insufficiency may result in a decreased utilization of amino acids which causes a compensatory increase in the rate of utilization of carbohydrate and fat; cortisone causes an increased utilization of amino acids followed by a sparing of carbohydrate and fat, thereby favoring their storage. The concept that the primary action of cortisone and related compounds is to stimulate gluconeogenesis from protein does not fully explain the extent of glycosuria or the insulin resistance that can be induced by these compounds (35). It seems necessary to assume that these hormones either stimulate gluconeogenesis from fat or that they inhibit some phase of carbohydrate utilization (oxidation, storage as glycogen or conversion to fat).

7. Effects upon specific tissues

The attention of laboratory and clinical investigators to the biologic effects of cortisone has centered on only a few tissues. There is no reason to assume that the effects of this and similar compounds are limited to any specific organ or tissue or that any tissue is unresponsive to them. There are probably gradients in the sensitivity of tissues to the cortical hormones and some tissues may be protected from the metabolic actions of these hormones to a greater extent than others by as yet unknown homeostatic mechanisms.

a. Lymphoid tissue. All of the known biologically active 11-oxygenated steroids of the adrenal cortex cause atrophy of the rat thymus when administered in high dosage. This has been found to be true of cortisone (65 and 135–138). Antopol (123) and Kochakian and Robertson (129) have noted thymus atrophy as the result of the administration of cortisone acetate in the mouse. It is now well established that the effects of the 11-oxysteroids upon lymph nodes and spleen are similar to, but less marked than, the regressive changes induced in thymus (65, 138, 139). According to Stoerk and Solotorovsky (139) the loss of thymic tissue during treatment with cortisone acetate is due to an increased destruction of lympho-

cytes, since the mitotic activity of the atrophic glands is undiminished. Heilman (140) studied the in vitro effects of cortisone and of 11-dehydrocorticosterone upon tissue cultures of lymph nodes. Each compound caused increased degeneration of the small and medium sized lymphocytes which are present in the migration zone. In a second study, Heilman (141) found that these same two compounds stimulated the migration of macrophages in tissue cultures of rabbit spleen.

Hechter and Johnson (142) observed that adrenal cortex extract was an effective lymphocytolytic agent in the presence of homogenates of lymphoid tissue but was ineffective in serum, blood or buffered saline solutions. Homogenates of brain also supported the lymphocytolytic activity of adrenal cortex extract. Cortisone and other active adrenal steroids were tested at the single dosage level of 10 micrograms per cc. without any lymphocytolytic activity in the presence of either lymphoid homogenate or serum. Schrek (143) found that adrenal cortex extracts, corticosterone and 17-hydroxycorticosterone each had an in vitro cytotoxic action on cells from the thymic gland of rabbits. Cortisone was not studied.

b. Blood lymphocytes. The lymphocytopenia that results from a variety of unrelated stresses may be due in major part to increased secretory activity of the adrenal cortices, although other factors may also be important. A decrease in blood lymphocytes follows the administration of adrenocorticotropic hormone, adrenal cortex extracts and 11-oxysteroids in laboratory animals. In their classic papers on this subject, Dougherty and White (144, 145) noted that cortisone was effective in causing lymphopenia in the adrenalectomized mouse. Antopol (123) has reported the production of lymphopenia as the result of cortisone acetate administration in the intact mouse. In 4 patients with Addison's disease given 100 mg. of cortisone acetate daily for five days, there was a transitory decrease in the number of lymphocytes with a small increase in neutrophils (41). Hills, Forsham and Finch (146) gave single intramuscular injections of 20 mg. of 17-hydroxycorticosterone to 5 patients with Addison's disease and observed an average fall of 42 per cent in the level of blood lymphocytes by four hours. Similar results on 7 patients were reported by Forsham *et al.* (147). During the protracted administration of cortisone acetate to patients with arthritis and related diseases, Sprague *et al.* (31) found no significant change in the level of lymphocytes either during or after the administration of the hormone. Significant decreases in lymphocytes during short periods of administration were observed in individual cases.

The in vitro effects of cortisone upon lymphocytes have been reviewed in an earlier section of this paper (permeability).

c. Blood eosinophils. Speirs and Meyer (148) found that eosinophils of

the adrenalectomized mouse are very sensitive to the 11-oxysteroids and are less sensitive to 11-desoxycorticosterone. As little as 3 micrograms of cortisone produced a 96 per cent decrease in eosinophils by four hours. Doses smaller than 1 microgram caused some degree of eosinopenia. Similar results have been obtained by Forsham (149).

The effect of cortisone upon the level of circulating eosinophils was first observed in human subjects. Hills, Forsham and Finch (146) showed that the number of circulating eosinophils is influenced by the activity of the pituitary-adrenocortical system. Five patients with Addison's disease were each given a single intramuscular injection of 20 mg. of 17-hydroxycorticosterone. There was an average fall of 63 per cent in the level of blood eosinophils by four hours. Similar results have been published by Forsham *et al.* (147). Conn (150) has observed that during the administration of 200 mg. of cortisone acetate daily for treatment of rheumatoid arthritis the level of blood eosinophils does not fall for forty-eight to seventy-two hours following the beginning of treatment. It was suggested that the insolubility of this compound may have been a factor in the delay. Perera *et al.* (43) administered 80 mg. per day of cortisone acetate to 5 patients and observed a definite fall in eosinophils in 3 of them. Thorn and Forsham (41) treated 4 patients with Addison's disease by the intramuscular injection of 100 mg. of cortisone acetate daily for five days and noted a fall of from 20 to 50 per cent in circulating eosinophils in 3 of them. When cortisone acetate was given intravenously in single doses of from 5 to 50 mg. in 9 patients, there was a significant drop in the level of eosinophils by four hours. Eliel, Pearson and White (151) administered 100 to 200 mg. of cortisone acetate daily for eighteen days to a patient with chronic lymphatic leukemia and noted eosinopenia during the course of treatment. Sprague *et al.* (31) found no significant change in the number of circulating eosinophils after the prolonged administration of cortisone acetate in their series of patients but did observe eosinopenia in some patients after short periods of treatment. It may be assumed that the effect of cortisone and of similar compounds upon the blood cells is either lost after a time or is masked by an increase in the rate of formation of these cells.

c. Antibodies. Dougherty, White and Chase (152) have presented evidence that an increase in the secretion of the 11-oxysteroids by the adrenal cortices releases stored immune bodies by causing fragmentation of lymphocytes (thymus, lymph nodes and circulation cells) thereby causing a rise in circulating antibody globulin. Stoerk and Solotorovsky (139) have observed small temporary rises in circulating antibodies as the result of the injection of adrenal cortex extracts in rabbits, but single injections of 10 mg. of cortisone acetate in previously immunized rabbits produced a fall of circulating antibodies in all instances. Since lymphoid tissue is be-

lieved to carry the antibody specific to the tuberculo-proteins, Stoerk (28) investigated the effect of cortisone acetate in the various types of hypersensitivity in guinea pigs. Hypersensitivity of the anaphylactic type was not prevented with cortisone acetate. It was found that pretreatment with cortisone acetate prevented the tuberculin reaction, due possibly to an increased rate of degradation of the antibody protein.

Mirick (153) has studied the effect of adrenocorticotropic hormone and of cortisone acetate upon the capacity of human subjects to produce antibodies. Four patients who were under treatment with cortisone acetate were vaccinated with a mixture of pneumoccocal polysaccharides. Antibodies were produced as promptly and in as high titer in patients receiving the steroid as in the controls. There was some suppression of the induced skin sensitivity to the pneumococcus polysaccharides during the administration of cortisone acetate.

d. Thyroid. Winter, Silber and Stoerk (65) administered 3 mg. of cortisone acetate daily to normal rats for a period of six weeks. The final average weight of the thyroid glands was slightly greater in the cortisone series than in the controls. Histologically, the thyroid appeared normal. Gabrilove and Soffer (154) noted that the administration of epinephrine suppresses the uptake of I^{131} by the thyroid gland of the intact rat but is followed by an increased collection of iodine by the thyroid of the adrenalectomized rat. When cortisone acetate is given with epinephrine to the adrenalectomized rat, the collection of iodine by the thyroid is similar to that noted in the intact rat given epinephrine alone.

Reiss, Forsham and Thorn (155) have described 8 patients with Addison's disease in which the subnormal gradients of I^{131} uptake were increased up to fourfold during the administration of 50 to 100 mg. of cortisone acetate daily. The effect was maximal after two to three days of treatment, and decreased thereafter. Sprague *et al.* (31) noted the case of 1 patient with rheumatoid arthritis whose basal metabolic rate was plus 16 per cent prior to the administration of cortisone acetate and fell to minus 3 per cent during treatment with the steroid. It was suggested that the change was related to the improvement in the arthritis rather than to a primary action of the hormone. In 2 other patients, there was no correlation between the changes in the metabolic rate and the administration of cortisone acetate.

e. Nervous system. Woodbury and Sayers (39) have observed that the administration of cortisone acetate (2 mg. daily) to the rat increases the excitability of the brain as measured by electroshock seizure threshold. Furthermore, cortisone acetate prevents the elevation in electroshock seizure threshold produced by 11-desoxycorticosterone acetate. According to Selye (156) cortisone is among the large number of steroid compounds

which have an "anesthetic" effect. This was manifest as a loss of the righting reflex in partially hepatectomized immature female rats which received intraperitoneal injections of steroids.

Thorn and Forsham (41) noted that patients with Addison's disease develop an increased sense of well-being and an increased appetite during treatment with cortisone acetate. The frequent occurrence of "euphoria", especially during the early stages of treatment with large doses of cortisone acetate or of adrenocorticotropic hormone has been confirmed by a number of clinical investigators (31, 48, 90, 157, 158). In a series of 21 rheumatoid patients given cortisone acetate, Hench *et al.* (48) observed increased appetite in 20 cases. The increase was very marked in 11 cases. Sprague *et al.* (31) noted 1 case of mental depression in a young female arthritic patient who was treated with cortisone acetate for 187 days. The change from a mild "euphoria" to depression occurred after nineteen weeks of therapy. The depression regressed when administration of the hormone was stopped.

In studies of patients with Addison's disease, Thorn and Forsham (41) found a progressive acceleration of brain waves with a return of the electroencephalogram towards normal during treatment with cortisone acetate.

f. Reproductive system. In earlier unpublished studies, the author found that large doses of cortisone (5 to 10 mg. daily) caused some regression of the testes in the adult male rat. In recent studies, the administration of 5 mg. of cortisone acetate daily failed to cause a significant loss in the weight of either the testes or seminal vesicles of the adult male rat. Winter, Silber and Stoerk (65) did not note any changes in the reproductive organs of male rats treated with 3 mg. of cortisone acetate daily for periods up to six weeks. Antopol (123) treated normal immature mice with 1.25 mg. of cortisone acetate per day for periods up to fifteen days and treated mature mice with 2.5 mg. of cortisone acetate per day for periods up to nineteen days. The testes, seminal vesicles and prostate were smaller than normal in the cortisone series, and the ovaries "appeared smaller."

Lactation generally fails in the adrenally insufficient rat. It was shown by Gaunt, Eversole and Kendall (159) that normal lactation can be sustained in adrenalectomized rats by the daily oral administration of 1 mg. of cortisone.

In the series of patients studied by Sprague *et al.* (31) 9 women had normal or almost normal menstrual function prior to the administration of cortisone acetate, and 3 of them became amenorrheic during treatment with this sterol. In the male patients, systematic inquiry about libido in 5 cases revealed that in 3 of them there was apparently a significant decrease in sexual drive and potency during the prolonged administration of cortisone acetate. The appearance of acne and hirsutism in some female patients

during the prolonged administration of cortisone acetate provided some indication that this compound either has weakly androgenic properties or that one of its metabolic products is androgenic.

g. Kidney. The effect of cortisone upon the renal excretion of electrolytes has been described in an earlier section of this review, and pathologic changes in the kidney will be described in the following section on tissue damage. The urinary excretion of cortisone and its metabolic products will not be considered, but the reader is referred to the excellent review by Mason and Engstrom (160).

Kendall (7) has stated that the adrenalectomized dog required 10 mg. of cortisone daily to sustain a normal renal function, *i.e.*, to excrete urea. Winter, Silber and Stoerk (65) studied the nitrogen, phosphorus and glycogen of the kidneys of rats treated with 3 mg. of cortisone acetate daily for six weeks. All values were within normal limits.

Beck *et al.* (161) observed a sharp rise in the urinary excretion of ascorbic acid during the first twenty-four hours of treatment with 75 to 100 mg. of adrenocorticotropic hormone in chronically diseased patients. No such increase was observed during the administration of 100 to 300 mg. of cortisone acetate. Ingbar *et al.* (162) have reported significant changes in renal function following administration of cortisone acetate to 4 adult males with normal kidney function. The dosage of cortisone acetate varied from 200 mg. daily for seven days to 1.6 Gm. in two days. The tubular secretion of PAH following load administration was increased up to 35 per cent with the steroid. There was little effect upon the clearance of either uric acid or creatinine. Deming and Luetscher (163) have studied the effects of cortisone acetate in nephrosis. The results varied from negligible changes to a complete remission of the nephrotic syndrome. An initial increase in proteinuria with a subsequent sharp fall was noted. Endogenous creatinine clearance was increased.

8. Anterior pituitary-adrenal cortex function

The mechanism whereby an excess of adrenal cortical hormones causes compensatory atrophy of the adrenal cortices was elucidated by Ingle and associates (164–167). The fact that large doses of cortisone cause compensatory atrophy of the adrenal cortices in normal rats was observed by Ingle and Mason (135) and by Wells and Kendall (136). Woodbury and Sayers (39) have demonstrated that cortisone acetate (2 mg. daily) will induce marked reduction in the weight and the concentration of ascorbic acid in the adrenal of the rat, changes in the gland which are characteristic of those which follow hypophysectomy. Stebbins (168) studied the cytochemical changes in the adrenal cortex of the rat following the administration of cortisone acetate. A dose of 3 mg. per day caused atrophy of the inner zones of the cortex and depletion of the lipoid and ketosteroid ma-

terial of these zones, but the glomerulosa remained unchanged. When the injections of the steroid were stopped, the changes were reversed so that the cortex again became normal in appearance. Winter, Silber and Stoerk (65) administered 3 mg. per day of cortisone acetate to young male rats for periods up to six weeks. The adrenal glands lost an average of 40 per cent of their weight by ten days and an average of over 50 per cent by six weeks. The regressive changes in the cortex were marked in the fascicular and reticular zones and slight in the glomerulosa. Following discontinuance of treatment, the reversal of the atrophic changes was evident at four days and after ten days the cortices appeared nearly normal. Antopol (123) has described compensatory atrophy of the adrenal cortex in the mouse given 1.25 to 2.5 mg. of cortisone acetate daily.

Among their series of classic studies on factors affecting pituitary adrenocorticotropic hormone (ACTH) response to stress, Sayers and Sayers (169) found that the administration of active principles of the adrenal cortex prior to a stress inhibited the release of ACTH. Cortisone and 17-hydroxycorticosterone were the highest in inhibitory potency.

Sprague *et al.* (31) presented 3 lines of evidence suggestive of a depression of adrenal cortical activity as a result of administering large doses of cortisone acetate to patients. First, several patients complained of weakness of varying degree which began a few days after the administration of cortisone acetate was stopped. Second, there was an abnormally low excretion of the 17-ketosteroids during the administration of, and after the withdrawal of the steroid. Third, there was a decrease in the eosinophil response to the administration of a single 25 mg. dose of ACTH. It was recognized by the authors that a direct action of cortisone upon the blood eosinophils may have altered the response to ACTH. Similar data on patients have been presented by Forsham *et al.* (170).

9. Tissue damage

Following the preparation of biologically active extracts of beef adrenal glands twenty years ago, the erroneous concept developed that hormones of the adrenal cortex do not damage the organism when administered in "high dosage." Adrenal cortex extracts have seldom been found toxic because it is difficult to administer doses which exceed the normal secretory activity of the adrenal cortices of either animals or patients. In the case of the crystalline compounds of the adrenal cortex, it is easily possible to administer dosages which cause damage to tissues.

Kochakian (171) and Kendall (122) each implanted pellets of cortisone in normal mice and noted the occurrence of cardiac and skeletal muscle lesions in these animals. Kendall described the lesions as areas of necrosis. In studies of the closely related compound, 17-hydroxycorticosterone given in doses of 5 mg. daily to normal rats, Ingle *et al.* (35) described deep

ulcers in the pyloric portion of the stomach in 2 rats. One of the rats had in addition several ulcers in the cecum with penetration of the wall in one area. Winter, Silber and Stoerk (65) observed only minor cellular damage in rats which received 3 mg. of cortisone acetate daily. Antopol (123) administered cortisone acetate in doses of 1.25 mg. daily to immature mice and 2.5 mg. daily to mature mice for periods up to nine days. In some cases, foci of necrosis and calcification were found in the hibernating bodies. The liver occasionally contained necrotic foci; granulomatous nodules were found in the liver, kidney and spleen in several animals. Such changes did not occur in the control mice.

Selye (47, 172) has found that the administration of cortisone acetate to unilaterally nephrectomized rats on a high sodium, high protein diet aggravates the renal damage caused by 11-desoxycorticosterone. In high dosage, cortisone acetate alone will cause damage. There is hyalinization of the glomerular capillaries and, eventually, an acute glomerulonephritis. Cortisone acetate causes very little cardiac damage even though the blood pressure rises. Cortisone acetate prevents certain other pathologic changes caused by 11-desoxycorticosterone in these animals. Thus, cortisone acetate prevents the development of mesenteric periarteritis nodosa and cures vessel lesions after they have fully developed in response to 11-desoxycorticosterone. The increase in erythrocyte sedimentation rate produced by the latter compound is counteracted by cortisone acetate. Although 11-desoxycorticosterone causes enlargement of the spleen and liver with little or no thymico-lymphatic involution, cortisone causes marked involution of the liver and all lymphatic organs.

Woodbury, Rosenberg and Sayers (173) have studied the effect of cortisone acetate alone, 11-desoxycorticosterone acetate alone and in combination with cortisone acetate, in unilaterally nephrectomized rats given 0.9 per cent sodium chloride to drink. Cortisone acetate (2 mg. daily for thirty-seven days) produces no observable pathologic changes in the pancreas, kidney or heart. On the contrary, 11-desoxycorticosterone acetate (twelve 15-mg. pellets per rat) induces marked pathologic changes in the pancreas (periarteritis nodosa), heart (interstitial myocarditis and periarteritis nodosa) and kidney (glomerulonephritis, hyalinization of glomeruli, interstitial nephritis and thickening of the renal vessels). Cortisone acetate (2 mg. daily) given simultaneously with 11-desoxycorticosterone acetate markedly inhibits the development of these pathologic changes.

Knowlton *et al.* (38) produced nephritis in rats by the injection of cytotoxic serum. The administration of cortisone acetate in doses of 5 and 2.5 mg. per day did not intensify the renal damage.

Other reports of tissue changes have been noted in other sections of this paper. Although it is possible to cause pathologic changes by the administration of very large amounts of cortisone to animals and damage is more

likely to occur under certain abnormal conditions, it seems probable that physiologic amounts and dosages equivalent to therapeutic doses in man do not cause any irreversible pathologic changes. It has not yet been possible to determine whether or not large doses of cortisone produce degenerative changes in man. None has been reported.

THERAPEUTIC EFFECTS OF CORTISONE

1. Addison's disease

The life expectancy of patients with Addison's disease has been considerably prolonged during the past twenty years, but about 50 per cent of these patients still die within seven years following the diagnosis of the disease (174). Moreover, during their survival, most of them do not show normal vigor. Although the value of injectable adrenal cortex extracts in treating this disease is well established, the cost of these preparations is too great to permit the continued administration of adequate dosage in most cases. The major gain in life expectancy for patients with adrenal cortical insufficiency dates from the introduction of 11-desoxycorticosterone acetate for clinical use. However, this compound does not fully replace the functional activity of the adrenal cortical secretions. Its deficiencies are likely to become evident when the patient is fasted or subjected to any other form of stress. From our knowledge of the biologic effects of cortisone in laboratory animals and in man, there is a rational basis for hope that cortisone will correct these deficiencies which are not rectified by 11-desoxycorticosterone. Cortisone has not yet been used in the treatment of clinical adrenal cortical insufficiency for periods sufficiently long to permit an appraisal of its effect upon the life expectancy of these patients.

A number of investigators have reported a striking improvement in the clinical condition of patients with Addison's disease treated with cortisone acetate (31, 41, 42, 43, 116). In a review of their experience in treating adrenally insufficient patients with cortisone acetate, Thorn *et al.* (42) noted striking clinical improvement during the intramuscular injection of 50 mg. or more daily for three to five days. There was relief of subjective symptoms, increase in vigor and appetite, feeling of warmth and an increased sense of well being. Following the initial injection of 100 mg. of cortisone acetate daily for three to five days, 5 patients were given subcutaneous implants of 3 to 10 pellets of cortisone acetate weighing 50 to 80 mg. each. The clinical improvement initiated by these large doses was sustained by absorption of cortisone from the pellets for periods of at least three months. Two of these 5 patients received a maintenance dose of 11-desoxycorticosterone acetate during the period of cortisone acetate therapy. These doses were not adequate to sustain the patients during periods of increased stress. Elsewhere, Thorn *et al.* (158) have stated that patients with complete adrenal insufficiency can be maintained with 10 to

20 mg. of cortisone acetate daily. The reviewer assumes that these doses of cortisone acetate are given in addition to a basic intake of 11-desoxycorticosterone acetate. Sprague (175) has a patient in whom adrenal cortical insufficiency developed following subtotal adrenalectomy for the relief of Cushing's syndrome. The patient was maintained for a time with 10 mg. of cortisone acetate daily without the addition of 11-desoxycorticosterone acetate. Subsequently the patient required additional treatment with 11-desoxycorticosterone acetate. A second patient with co-existing Addisons' disease and diabetes was treated with 25 mg. of cortisone acetate three times weekly, plus 2 mg. of 11-desoxycorticosterone acetate daily. When treated with the latter compound only, her insulin requirement was as low as 7 units daily. With the addition of cortisone acetate, the insulin requirement was increased to 50 or 60 units daily which was essentially the same as her requirement prior to the onset of Addison's disease.

2 Rheumatoid arthritis

As the result of careful studies of conditions which favor remission in rheumatoid arthritis, such as pregnancy, hepatitis with jaundice, surgery and starvation, it was postulated by Hench and Kendall of the Mayo Clinic that the secretory activity of the adrenal cortices must be stimulated in each of these conditions and might play a role in causing the remissions. When sufficient amounts of cortisone became available in the fall of 1948, studies of its effects in arthritis were undertaken by these investigators. Their announcement of the favorable effect of cortisone and of adrenocorticotropic hormone upon rheumatoid arthritis in April of 1949 further emphasized the potential reversibility of this disease, led to the testing of these and chemically related compounds in other "collagen diseases," and thereby opened a vast new field for clinical and laboratory investigations.

The preliminary report of Hench *et al.* (176) was based upon the effects of cortisone and cortisone acetate in 14 severe or moderately severe cases of chronic polyarticular rheumatoid arthritis of four and one half months' to five years' duration. None of these patients had responded to previous therapy. An initial dose of 300 mg. of cortisone acetate followed by 100 mg. per day by intragluteal injection was effective in reducing the pain, tenderness and stiffness. Articular and muscular function was improved, and the elevated sedimentation rates decreased to normal values. The beginning of improvement was noted within a few days, often within forty-eight hours. When the administration of cortisone was stopped, the symptoms of arthritis promptly reappeared.

Hench *et al.* (48) have recently reviewed their further experiences with the use of cortisone acetate and of adrenocorticotropic hormone in the treatment of rheumatoid arthritis. Among the 21 rheumatoid patients

treated with cortisone acetate, 12 had very marked, 8 had marked, and 1 had moderate antirheumatic effects. These studies involved a total of 35 courses of cortisone acetate varying from 8 to 187 days in duration. Individual doses ranged from 25 to 300 mg. daily, but the average effective daily dose was approximately 100 mg. of cortisone acetate per day. The course of improvement generally followed a characteristic pattern: reduction of stiffness, then of pain on motion, and finally of tenderness and swelling. Some patients became symptom-free, but others retained minor degrees of rheumatic activity. The fever, when present, was promptly reduced by the administration of cortisone acetate, sedimentation rates were reduced to normal in 15 cases, to almost normal in 3 and to intermediate values in 3 cases. When treatment was stopped, the symptoms of arthritis generally reappeared promptly, but a few cases remained in remission for periods of two weeks to a few months. In 2 patients the remissions were maintained for ten and twelve months, which was up to the time of the last report. Symptoms of hypercorticism such as mild acne, hirsutism, rounding of the face and transient edema developed during the treatment of some patients. Eight patients did not show any significant side effects. The incidence of very marked undesirable effects was less than 20 per cent.

Boland and Headley (177) treated 5 patients with severe rheumatoid arthritis by administering 1,000 mg. of cortisone acetate to each in divided doses over eight days. All of the patients improved rapidly but there was a prompt relapse upon stopping treatment in 4 of the 5 cases. In 1 patient the disease was still in partial remission two months after stopping treatment. Three patients with less severe rheumatoid arthritis were adequately but not completely controlled on doses of 50 mg. of cortisone acetate daily; 50 mg. every other day was less effective. In each of the 8 patients, the sedimentation rate was reduced during treatment with cortisone acetate. A preliminary report on the use of cortisone acetate and of ACTH in rheumatoid arthritis has been made by the Rheumatoid Arthritis Research Group of Michael Reese Hospital (178). Three patients were treated with cortisone acetate and responded in a manner similar to those reported from the Mayo Clinic. In 1 patient, the usual maintenance dose in rheumatoid arthritis, namely 100 mg. per day, had to be doubled in order to maintain clinical improvement and reduce the sedimentation rate to normal.

Bauer and associates (179) reported separately on a total of 9 cases of rheumatoid arthritis or spondylitis which were treated with cortisone acetate for only a few days. Marked improvement occurred during the time of treatment in each case. Hollander (180) has given a report on 29 cases of rheumatoid arthritis treated with cortisone acetate or with adrenocorti-

cotropic hormone. The details of treatment were not given, but it was stated that benefit was seen in each patient during the time the hormone was administered. No lasting remissions were observed after stopping treatment.

Freyberg (181) has summarized his experiences with cortisone acetate in the treatment of 17 cases of rheumatoid arthritis and has reviewed the published and unpublished findings of others. It is stated that until 1950, cortisone acetate had been used in about 160 patients with chronic rheumatic disease. Cortisone acetate has three major therapeutic effects in this disease: a) reduction in stiffness of the joint, b) relief of pain, and c) decrease in joint inflammation. The destructive changes in cartilage and bone are not altered. The dosage required to secure remission of the disease is about 100 mg. daily. At least in some patients, remission can be maintained with 100 mg. of cortisone acetate three times weekly.

3. Other types of arthritis

Hench *et al.* (48) have described 1 patient with severe psoriasis and moderately severe psoriatic arthritis who received 100 mg. of cortisone acetate daily for forty-three days. During treatment, the arthritis disappeared promptly and the psoriasis improved slowly. Two patients with tuberculous monarthritis of a knee received cortisone acetate. During each of 2 courses of 100 mg. of cortisone acetate daily, 1 patient had disappearance of the stiffness, tenderness and pain of the knee, but biopsy showed that the disease remained bacteriologically active. When treatment was stopped, the symptoms returned. A similar response to cortisone acetate occurred in the second case. One patient with osteoarthritis and chronic lymphatic leukemia was treated with cortisone acetate for eighteen days. The symptoms of the arthritis disappeared and had not returned one month later. The blood counts remained unchanged during treatment. One patient with chronic ulcerative colitis had a complicating subacute polyarthritis. Cortisone acetate was given for thirty-six days. The remission of the arthritis lasted over four months.

4. Acute rheumatic fever

Hench *et al.* (182) made a preliminary report on the therapeutic effects of cortisone acetate in 3 young patients in the acute phase of rheumatic fever. More recently, Hench *et al.* (48) and Barnes and Smith (183) have reported on 7 patients treated with cortisone acetate at the Mayo Clinic. The initial dose of cortisone acetate was usually 200 mg. daily and was later reduced to 100 mg. and continued for twenty-two to forty days. The fever disappeared within one to six days, and the acute polyarthritis in two to eleven days. The sedimentation rates were reduced to normal, and the tachycardia disappeared. When treatment was stopped, mild

rheumatic recurrences appeared in 3 patients but disappeared when treatment was renewed and did not return when treatment was withdrawn the second time. No evidence of rheumatic carditis was found at the time of writing. Similar observations on 2 patients with rheumatic fever treated with cortisone acetate were published by McEwen *et al.* (184). The effects of the hormone on the carditis of these patients were equivocal. The involvement of the heart was well established prior to the beginning of therapy.

5. Gout

Adrenocorticotropic hormone has been used successfully in the treatment of gout and of gouty arthritis (48) but there are no published reports on the use of cortisone in this disease. There are unpublished reports that cortisone has been used successfully in relieving the symptoms of gouty arthritis, but the details are not known to the reviewer.

6. Lupus erythematosus disseminatus

Hench *et al.* (48) found that cortisone acetate had a favorable effect on several patients with severe disseminated lupus erythematosus but details were not reported. Baehr and Soffer (185) have used cortisone acetate and adrenocorticotropic hormone in the treatment of 5 patients who were critically ill with disseminated lupus erythematosus. The effective therapeutic dose was 150 to 200 mg. per day. Improvement occurred within forty-eight hours with a feeling of well being, strength and relief of arthralgia. Subsequently, there was a fall in temperature, subsidence of gallop rhythm and tachypnea, healing of mouth lesions, relief of joint pains and swelling and disappearance of pleuritis and pericarditis. There was persistence of the leukopenia and elevated sedimentation rate.

7. Periarteritis nodosa

Shick, Baggenstoss and Polley (186) used cortisone acetate in the treatment of 3 patients who were critically ill with periarteritis nodosa. All of the patients showed an initial improvement which included prompt subjective relief, reduction of fever and a gradual reduction of the sedimentation rate. Two of the patients died with renal and cardiac failure, after 75 and 146 days. Necropsy showed complete healing of the arterial lesions, but fibrous obliteration of the lumens of these vessels had occurred, resulting in a widespread visceral infarction.

8. Cranial arteritis

Shick, Baggenstoss and Polley (186) administered cortisone acetate to 2 patients with cranial arteritis and observed prompt reversal of symptoms.

9. Asthma and hay fever

Hench *et al.* (48) noted that the hay fever of 2 rheumatoid patients was relieved during treatment with cortisone acetate. They indicated that cortisone acetate has a useful effect in asthma and other allergic conditions, but no details were reported.

10. Neoplastic diseases

Pearson *et al.* (90) have reported on 6 patients with lymphomatous tumors who were treated with cortisone acetate and with adrenocorticotropic hormone. There was involution of the lymphoid masses within six days after initiation of cortisone acetate administration. The decrease in the size of lymph nodes and of the enlarged spleens was progressive during treatment. In a later report (187), it was stated that in all of these patients, regrowth of the tumor masses became evident within ten days to three months after stopping therapy. Three patients, 2 with leukemia and 1 with lymphosarcoma, have shown a second response to therapy. In further studies of the effects of cortisone acetate and adrenocorticotropic hormone, no effect on tumor growth was observed in 6 patients—1 each with carcinoma of the breast, carcinoma of the testis or adrenal, Ewing's tumor, plasma cell myeloma, rhabdomyosarcoma and carcinoma of the pancreas. Eliel, Pearson and White (151) have reported a case of chronic lymphatic leukemia treated with 100–200 mg. daily of cortisone acetate for eighteen days. Marked regression of the lymph nodes and spleen occurred during treatment, but regrowth occurred when the injections were stopped.

11. Other diseases

There are word-of-mouth reports that cortisone acetate has been found to be of value in the treatment of scleroderma, ulcerative colitis, pemphigus, Loeffer's pneumonia and nonspecific iritis, but no published data have been found by the reviewer.

UNFAVORABLE EFFECTS OF CORTISONE

The prolonged administration of large doses (100 mg. or greater per day) of cortisone causes unfavorable effects in some patients. Some of these changes have been reviewed in other sections of this paper. The signs of cortisone excess are similar to and probably identical with the symptoms of Cushing's syndrome. These include impairment of carbohydrate tolerance, weakness and wasting of muscle, osteoporosis, striation of the skin, tendency to bruise, changes in facial contour, acne and hirsutism, alkalosis, etc.

The most complete reports on the unfavorable effects of cortisone acetate in man are by Sprague *et al.* (31) and by Hench *et al.* (48). Among the

patients studied at the Mayo Clinic, a number exhibited rounding of the facial contours as an early sign of cortisone excess. Acne and hirsutism were pronounced in only 1 woman who received the hormone for 187 days. Thinning of the skin with development of striae was observed in 6 patients treated with cortisone acetate. Muscular weakness and signs of reduced gonadal activity appeared in some of the patients. In 1 patient a psychosis (depression) developed during treatment. Of 21 patients with rheumatoid arthritis who were treated with cortisone acetate, 8 manifested no unfavorable effects, moderate reactions appeared in about the same percentage and moderate to marked reactions were seen in about 20 per cent of the group. In general, the undesirable effects were marked in those patients who received 200 mg. of cortisone acetate per day.

The observations of other clinical investigators are in accord with the above reports from the Mayo Clinic.

DISCUSSION

This review is primarily a compilation of the available references on the biologic and therapeutic effects of cortisone. It should be noted that cortisone, which was isolated from adrenal cortex extracts, was used in all earlier studies and that recent and current studies use cortisone acetate, which has been prepared by partial synthesis. It is too early to appraise many of the recent developments in the clinical use of cortisone or to find any satisfactory explanation for its mode of action. At a later time a more critical, selective and interpretative treatment of the published data will be in order.

If any one fact has been made evident about cortisone, it is that this substance affects many different tissues and physiologic processes of the body. At a time when the physiology of the adrenal cortex seemed more simple, cortisone and related 11-oxygenated steroids were tagged as "S" or "sugar hormones" or "glucocorticoids." The author is not without sin in this matter of describing an elephant in terms of the shape of its tail and was among the students of endocrinology who found these characterizations useful, but he believes that this is an appropriate time to abandon the concept that cortisone is concerned principally with carbohydrate metabolism and to explore each of its many biologic properties in search for new concepts of its action. As an antidote for an era of oversimplification in adrenal physiology, the author recommends the masterful review of the adrenal cortex and homeostasis by Sayers (188). The consequences of cortical hormone action spread through the organism in a manner reminiscent of the waves caused by the impact of a stone in a pool of water, but the point of impact of the hormone remains unknown for the present.

The search for an explanation of the favorable therapeutic effects of cortisone in the treatment of arthritis and related diseases has gone in the following directions: a) cortisone inhibits the action of hyaluronidase which is thought to play a role in the etiology of rheumatoid diseases; b) cortisone has been found to inhibit the granulation of injured tissues in experimental animals, an effect that may relate to its action upon the mesenchymal diseases in man; c) certain types of hypersensitivity phenomena are inhibited by cortisone—connective tissue diseases may result from allergic or other types of hypersensitivity of connective tissues; and d) cortisone inhibits inflammatory reactions, possibly by blocking or destroying the substance or substances causing inflammation. These four lines of search for an explanation of the therapeutic effects of cortisone overlap, especially the third and fourth.

The story of cortisone and of adrenocorticotropic hormone as applied to medicine (48) (189) is based upon essential contributions from several sources: a) the chemists who isolated and characterized these substances, b) the clinical investigator who believed that rheumatoid arthritis was reversible, c) the laboratory investigator whose understanding of the biologic properties of cortisone led him and the clinical investigator to plan its test in arthritis, d) the chemists who developed practical methods for the production of these hormones, and e) the research and business administration of two private industries who assumed a costly risk in their farsighted and courageous decision to make adequate amounts of these hormones available for clinical investigations. This and many other examples support the thesis that the large-scale laboratory and clinical testing of natural and synthetic products for favorable effects upon a disease is a very important approach to experimental medicine. However, the philosophy that the chemist should first make a drug and then search for a disease which it will cure should not be permitted to replace or submerge research on the fundamental mechanisms of the disease. Surely both approaches will remain important and can coexist.

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The Association for the Study of Internal Secretions

LETTER TO THE EDITOR

To the Editor:

Through you I should like to discuss with your readers, and particularly with the members of the Association for the Study of Internal Secretions, the type of program which we are planning for Atlantic City in June of 1951.

At our meeting in San Francisco we voted to have three days of scientific programs, rather than the two we have had in the past. Dr. Robert Williams, of Seattle, Washington, wrote and suggested that we try grouping the papers under separate headings, and this suggestion met with favor in the Council meeting.

Accordingly, we have made arrangements for Thursday, Friday, and Saturday, June 7, 8, and 9, the meetings to be held either in the Chalfonte or Haddon Hall hotels. Tentatively, we are suggesting the following schedule:

Thursday: 9:30 A.M.—General subjects.
2:00 P.M.—Papers relating to the pituitary body.
8:00 P.M.—"Information Please," a program of informal discussion, with the audience and a "Board of Experts" taking part.

Friday: 9:00 A.M.—Papers relating to the thyroid and parathyroid glands.
2:00 P.M.—Papers relating to the adrenal glands.
Evening —The annual cocktail party and banquet.

Saturday: 9:00 A.M.—Papers relating to gonads and sterility.
2:00 P.M.—Joint session with the American Diabetes Association.

For each of these sessions there will be two presiding officers; one interested principally in clinical medicine, the other in experimental studies. These doctors will be responsible for the selection of papers for their own program, the title and abstracts being sent to them by the chairman of the Program Committee.

This letter is accompanied by instructions for the submission of abstracts. These instructions were prepared by Dr. Edward Doisy. Last year he and his associates and their secretaries had several weeks of needless work due to the incompleteness of information. Dr. Jane Russell, School of Medicine, Emory University, Georgia, is chairman of the Program Committee for 1951. We are particularly desirous of having more papers relating to clinical medicine submitted for these programs. The early submission of titles and complete abstracts will greatly facilitate planning of our meeting. Because so many members of the Program Committee will need to review these abstracts, we must continue to ask for four copies. No abstracts received after *March 1, 1951*, can be considered.

We are going to try this three-day meeting for 1951. The course to be followed in subsequent years will be determined by vote at the annual meeting at the conclusion of this program.

E. H. RYNEARSON, M.D., *President*

THE 1951 ANNUAL MEETING

The Thirty-third Annual Meeting of the Association for the Study of Internal Secretions will be held at the Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey. The Scientific Sessions have been extended to three days, Thursday, Friday, and Saturday, June 7-8-9.

The Local Chairman of Arrangements is Dr. Matthew Molitch.

Due to the advance in the date of our meeting, Chalfonte-Haddon Hall Hotel will be unable to accommodate all of our members by reason of a previous commitment. The Colton Manor, on Pennsylvania Avenue near Haddon Hall, is an excellent hotel, which has been recently refurnished, and is holding one hundred rooms for our members on the "first come, first served" basis. The Hotel Strand, at Pennsylvania Avenue and the Boardwalk, has also promised to supply a limited number of rooms. It is important that reservations be made immediately if you are to avoid disappointment.

All Scientific Sessions will be held in the Chalfonte-Haddon Hall Hotel. The rooms, in which the session will be held, will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, June 8, at 7:30 P.M. in the Rutland Room, preceded by cocktails at 6:30 P.M. in the adjoining Benjamin West Room.

Those wishing to present papers, which will be limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Jane Russell, School of Medicine, Emory University, Atlanta, Georgia, not later than *March 1, 1951. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and journals of the*

Association. The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.
2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each non-member author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of non-members who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *i.e.*, M.D., of each author should be given after his name.
   Line 3. Institution of origin and city in which institution is located.
3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter-perfect, since there will be no opportunity for proof reading by authors.

Nominations for the Ayerst, McKenna and Harrison Fellowship, the Schering Fellowship in Endocrinology, and the Squibb and Ciba Awards should be made on special application forms, which may be obtained from the Secretary-Treasurer, Henry H. Turner, M.D., 1200 North Walker Street, Oklahoma City 3, Oklahoma, and filed with the Secretary not later than *March 15, 1951.*

THE 1951 AWARDS AND FELLOWSHIPS

Fellowships

THE AYERST McKENNA AND HARRISON FELLOWSHIP

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected for the Fellowship in 1949, and the 1950 Fellowship was awarded to Dr. Lawrence E. Shulman.

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

The Schering Fellowship in Endocrinology was established in 1949 and the first recipient was Dr. D. Laurence Wilson, who also received the 1950 Fellowship.

Association Fellowships are designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $2,500.00, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 or 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Awards

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb & Sons Award of $1,000.00 was established in 1929, and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr E. A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; in 1949 to Dr. Herbert M. Evans; and in 1950 to Dr. C. N. H. Long. In 1943 no award was given. A special committee of five members of the Association selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

THE CIBA AWARD

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than thirty-five years of age in the field of clinical or preclinical endocrinology was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; in 1949 to Dr. George Sayers; and in 1950 to Dr. Oscar M. Hechter. The Award is for $1,200.00. If within twenty-four months of the date of the Award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $1,800.00.

NOMINATIONS

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the *Secretary, Dr. Henry H. Turner,* 1200 North Walker Street, Oklahoma City 3, Oklahoma, and returned to him *not later than March 15, 1951.*

The American Goiter Association

THE 1951 ANNUAL MEETING

The next Annual Meeting of the American Goiter Association will be held in Columbus, Ohio, May 24, 25 and 26, 1951, at the Deshler Wallick Hotel.

VAN METER PRIZE AWARD FOR 1951

THE American Goiter Association again offers the Van Meter Prize Award of three hundred dollars, and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Columbus, Ohio, May 24, 25, 26, 1951, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy in duplicate sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, *not later than March 1, 1951.* The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

CLEVELAND MEETING

DECEMBER 26–30, 1950

The 117th Meeting of the American Association for the Advancement of Science, the annual meeting for the year 1950, will be a full-scale meeting—with programs in every principal field of science. All 17 of the Association's sections and subsections, and more than 40 participating societies and organizations, are completing plans for an aggregate of more than 200 sessions.

There will be a considerable number of outstanding symposia. The list of special sessions includes the AAAS Presidential Address, and addresses sponsored by the Academy Conference, the National Geographic Society, the Scientific Research Society of America, the Society of the Sigma Xi, and the United Chapters of Phi Beta Kappa.

An extensive series of tours to museums, laboratories, and industrial plants of the Cleveland area has been planned. Some of these will be of particular interest to chemists and are being included as a part of the program of Section C.

The Annual Science Exposition, in the Arena of Cleveland's Public Auditorium—with some 150 booths—will be almost twice as large as that of the New York Meeting. In the Exposition, publishers, supply houses, microscope manufacturers, instrument makers, and industrial concerns will exhibit their latest products and portray their technical accomplishments on a scale impossible at a smaller meeting in a single scientific field. Adjacent to the exhibit area will be the Main registration, the Visible Directory of Registrants, the annual Photography-in-Science Salon, sponsored by *The Scientific Monthly* and the Smithsonian Institution, and the Science Theatre—throughout the week, repeating programs of the most recent scientific films.

An outline of the sectional programs of special interest to endocrinologists follows (numbers are *dates* in December):

Section C—Chemistry:

Twelve sessions: a) two on steroid hormones, 28; b) two on ballistics, 30; c) two on insecticides, 30; d) one on medicinal chemistry, 29; e) five, of general papers, 27, 29; chemists' luncheon, 30.

Section F—Zoological Sciences:

Symposium on "Genetics and Behavior," 29.

Subsection Nm—Medicine:

Four-session symposium on "Biological Effects of Radiation," 29, 30.

Subsection Nd—Dentistry:

Four sessions on dental research of all governmental agencies, 29, 30.

Subsection Np—Pharmacology:

Four sessions—joint program with Scientific Section, American Pharmaceutical Association, 28, 29.

Full details of these programs, with speakers and dates, will appear in *Science* at a later date.

Housing and Registration

The hotels of Cleveland have pledged themselves to provide ample housing for those attending the 117th Meeting. Housing will be taken care of by the experienced personnel of the Cleveland Convention Bureau, with hotels confirming reservations directly. Announcements and coupons for reservations will appear in *Science* and *The Scientific Monthly*, beginning the last of August. The hotels include the Statler (headquarters of the AAAS), the Hollenden, the Carter, the Allerton, the Olmsted, and the Auditorium Hotel—the last particularly convenient for exhibitors.

At the New York Meeting, the Council of the Association voted overwhelmingly to continue with advance registration. Plans are already made to ensure the mailing of the General Program to advance registrants not later than December 1 (as compared with December 6–9 last year), *by first class mail.*

RAYMOND L. TAYLOR,
Assistant Administrative Secretary
AAAS
1515 Massachusetts Avenue, N.W.
Washington, D.C.

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The 1950 Convention will be held in the Hotel Statler, New York City, November 9 through 11. The program will deal with civil defense, the defense role of the physician, aviation medicine, rehabilitation, military medicine, surgery, sanitation, and discussions on the use of the newest therapeutic and prophylactic agents in emergency conditions.